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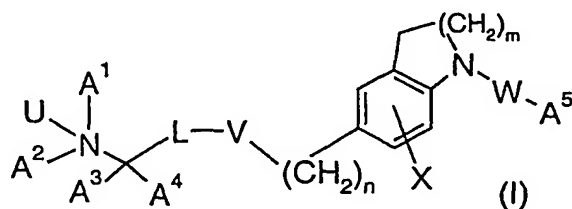
(54) Title: DIHYDROINDOLE AND TETRAHYDROQUINOLINE DERIVATIVES

(57) Abstract: The present invention relates to compounds of formula (I) wherein U, A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup>, A<sup>4</sup>, L, V, W, X, m and n are as defined in the description and claims, and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with 2,3-oxidosqualene-lanosterol cyclase such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

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## DIHYDROINDOLE AND TETRAHYDROQUINOLINE DERIVATIVES

The present invention is concerned with novel dihydroindole and tetrahydroquinoline derivatives, their manufacture and their use as medicaments. In particular, the invention relates to compounds of the formula (I)



5 wherein

U is O or a lone pair,

V is a) O, S, NR<sup>1</sup>, or CH<sub>2</sub>, and L is lower-alkylene or lower-alkenylene,  
b) -CH=CH- or -C≡C-, and L is lower-alkylene or a single bond,

W is CO, COO, CONR<sup>2</sup>, CSO, CSNR<sup>2</sup>, SO<sub>2</sub>, or SO<sub>2</sub>NR<sup>2</sup>,

10 X is hydrogen or one or more optional halogen and/or lower-alkyl substituents,

m is 1 or 2,

n is 0 to 7,

A<sup>1</sup> is hydrogen, lower-alkenyl, or lower-alkyl optionally substituted by hydroxy, lower-alkoxy, or thio-lower-alkoxy,

15 A<sup>2</sup> is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower-alkinyl, or lower-alkyl optionally substituted by hydroxy, lower-alkoxy or thio-lower-alkoxy,

A<sup>3</sup> and A<sup>4</sup> independently from each other are hydrogen or lower-alkyl, or

A<sup>1</sup> and A<sup>2</sup> or A<sup>1</sup> and A<sup>3</sup> are bonded to each other to form a ring and -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- are lower-alkylene or lower-alkenylene, optionally substituted by R<sup>3</sup>, in  
20 which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- can optionally be replaced by NR<sup>4</sup>, S, or O,

A<sup>5</sup> is cycloalkyl, cycloalkyl-lower-alkyl, heterocycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, lower-alkyl optionally substituted with hydroxy or lower-alkoxy, alkenyl optionally substituted with  
25 hydroxy, or alkadienyl optionally substituted with hydroxy,

R<sup>3</sup> is hydroxy, lower-alkoxy, thio-lower-alkoxy, N(R<sup>5</sup>,R<sup>6</sup>), or lower-alkyl optionally substituted by hydroxy,

R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> independently from each other are hydrogen or lower-alkyl, and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

5 The compounds of the present invention inhibit 2,3-oxidosqualene-lanosterol cyclase (EC 5.4.99.) which is required for the biosynthesis of cholesterol, ergosterol and other sterols. Causal risk factors that directly promote the development of coronary and peripheral atherosclerosis include elevated low-density lipoprotein cholesterol (LDL-C),  
10 low high-density lipoprotein cholesterol (HDL-C), hypertension, cigarette smoking and diabetes mellitus. Other synergistic risk factors include elevated concentrations of triglyceride (TG)-rich lipoproteins, small, dense low-density lipoprotein particles, lipoprotein (a) (Lp(a)), and homocysteine. Predisposing risk factors modify the causal or conditional risk factors and thus affect atherogenesis indirectly. The predisposing risk factors are obesity, physical inactivity, family history of premature CVD, and male sex. The  
15 strong connection between coronary heart disease (CHD) and high LDL-C levels in plasma, and the therapeutic advantage of lowering elevated LDL-C levels are now well established (Gotto et al., *Circulation* 81, 1990, 1721-1733; Stein et al., *Nutr. Metab. Cardiovasc. Dis.* 2, 1992, 113-156; Illingworth, *Med. Clin. North. Am.* 84, 2000, 23-42). Cholesterol-rich, sometimes unstable, atherosclerotic plaques lead to the occlusion of  
20 blood vessels resulting in an ischemia or an infarct. Studies with respect to primary prophylaxis have shown that a lowering of plasma LDL-C levels in plasma reduces the frequency of non-fatal incidences of CHD, while the overall morbidity remains unchanged. The lowering of plasma LDL-C levels in patients with pre-established CHD (secondary intervention) reduces CHD mortality and morbidity; meta-analysis of different  
25 studies shows that this decrease is proportional to the reduction of the LDL-C (Ross et al., *Arch. Intern. Med.* 159, 1999, 1793-1802).

The clinical advantage of cholesterol lowering is greater for patients with pre-established CHD than for asymptomatic persons with hypercholesterolemia. According to current guidelines, cholesterol lowering treatment is recommended for patients who had  
30 survived a myocardial infarct or patients suffering from angina pectoris or another atherosclerotic disease, with a target LDL-C level of 100 mg/dl.

Preparations such as bile acid sequestrants, fibrates, nicotinic acid, probucol as well as statins, i.e. HMG-Co-A reductase inhibitors such as simvastatin and atorvastatin, are used for usual standard therapies. The best statins reduce plasma LDL-C effectively by at  
35 least 40%, and also plasma triglycerides, a synergistic risk factor, but less effectively. In contrast, fibrates reduce plasma triglycerides effectively, but not LDL-C. Combination of a

statin and a fibrate proved to be very efficacious in lowering LDL-C and triglycerides (Ellen and McPherson, *J. Cardiol.* 81, 1998, 60B-65B), but safety of such a combination remains an issue (Shepherd, *Eur. Heart J.* 16, 1995, 5-13). A single drug with a mixed profile combining effective lowering of both LDL-C and triglycerides would provide  
5 additional clinical benefit to asymptomatic and symptomatic patients.

In humans, statins are well tolerated at standard dosage, but reductions in non-sterol intermediates in the cholesterol synthesis pathway, such as isoprenoids and coenzyme Q, may be associated with adverse clinical events at high doses (Davignon et al., *Can. J. Cardiol.* 8, 1992, 843-864; Pederson and Tobert, *Drug Safety* 14, 1996, 11-24).

10 This has stimulated the search for, and development of compounds that inhibit cholesterol biosynthesis, yet act distal to the synthesis of these important, non-sterol intermediates. 2,3-oxidosqualene:lanosterol cyclase (OSC), a microsomal enzyme, represents a unique target for a cholesterol-lowering drug (Morand et al., *J. Lipid Res.*, 38, 1997, 373-390; Mark et al., *J. Lipid Res.* 37, 1996, 148-158). OSC is downstream of  
15 farnesyl-pyrophosphate, beyond the synthesis of isoprenoids and coenzyme Q. In hamsters, pharmacologically active doses of an OSC inhibitor showed no adverse side-effects, in contrast to a statin which reduced food-intake and body weight, and increased plasma bilirubin, liver weight and liver triglyceride content (Morand et al., *J. Lipid Res.*, 38, 1997, 373-390). The compounds described in European Patent Application No. 636  
20 367, which inhibit OSC and which lower the total cholesterol in plasma, belong to these substances.

OSC inhibition does not trigger the overexpression of HMGR because of an indirect, negative feed-back regulatory mechanism involving the production of 24(S),25-epoxycholesterol (Peffley et al., *Biochem. Pharmacol.* 56, 1998, 439-449; Nelson et al., *J. Biol. Chem.* 256, 1981, 1067-1068; Spencer et al., *J. Biol. Chem.* 260, 1985, 13391-13394; Panini et al., *J. Lipid Res.* 27, 1986, 1190-1204; Ness et al., *Arch. Biochem. Biophys.* 308, 1994, 420-425). This negative feed-back regulatory mechanism is fundamental to the concept of OSC inhibition because (i) it potentiates synergistically the primary inhibitory effect with an indirect down-regulation of HMGR, and (ii) it prevents the massive  
30 accumulation of the precursor monooxidosqualene in the liver. In addition, 24(S),25-epoxycholesterol was found to be one of the most potent agonists of the nuclear receptor LXR (Janowski et al., *Proc. Natl. Acad. Sci. USA*, 96, 1999, 266-271). Considering that 24(S),25-epoxycholesterol is a by-product of inhibition of OSC it is hypothesized that the OSC inhibitors of the present invention could also indirectly activate LXR-dependent  
35 pathways such as (i) cholesterol-7 $\alpha$ -hydroxylase to increase the consumption of cholesterol via the bile acid route, (ii) expression of ABC proteins with the potential to stimulate reverse cholesterol transport and increase plasma HDL-C levels (Venkateswaran



et al., J. Biol. Chem. 275, 2000, 14700-14707; Costet et al., J. Biol. Chem. June 2000, in press; Ordovas, Nutr Rev 58, 2000, 76-79, Schmitz and Kaminsky, Front Biosci 6, 2001, D505-D514), and/or inhibit intestinal cholesterol absorption (Mangelsdorf, XIIth International Symposium on Atherosclerosis, Stockholm, June 2000). In addition, possible  
5 cross talks between fatty acid and cholesterol metabolism mediated by liver LXR have been hypothesized (Tobin et al., Mol. Endocrinol. 14, 2000, 741-752).

The present compounds of formula I inhibit OSC and therefore also inhibit the biosynthesis of cholesterol, ergosterol and other sterols, and reduce the plasma cholesterol levels. They can therefore be used in the therapy and prophylaxis of hypercholesterolemia,  
10 hyperlipemia, arteriosclerosis and vascular diseases in general. Furthermore, they can be used in the therapy and/or prevention of mycoses, parasite infections, gallstones, cholestatic liver disorders, tumors and hyperproliferative disorders, e.g. hyperproliferative skin and vascular disorders. In addition, it has unexpectedly been found that the compounds of the present invention can also be of therapeutical use to improve glucose  
15 tolerance in order to treat and/or prevent related diseases such as diabetes. The compounds of the present invention further exhibit improved pharmacological properties compared to known compounds.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

20 In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term "lone pair" refers to an unbound electron pair, in particular to the unbound electron pair of a nitrogen atom in e.g. an amine.

25 The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

The term "protecting group" refers to groups such as acyl, azoyl, alkoxycarbonyl, aryloxycarbonyl, or silyl. Examples are e.g. t-butyloxycarbonyl, benzyloxycarbonyl or fluorenylmethyloxycarbonyl which can be used for the protection of amino groups or trimethylsilyl, dimethyl-tert.-butyl-silyl or tert.-butyl-diphenyl-silyl, which can be used for  
30 the protection of hydroxy groups, trityl or p-methoxybenzyl for sulfur, methyl or benzyl for the protection of phenole derivatives, methyl, ethyl or tert.-butyl for the protection of thiophenole derivatives.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty

carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms. Lower-alkyl groups as described below also are preferred alkyl groups. Alkyl groups can be substituted e.g. with halogen, hydroxy, lower-alkoxy, thio-lower-alkoxy, lower-alkoxy-carbonyl,  $\text{NH}_2$ , and/or  $\text{N}(\text{lower-alkyl})_2$ .

5       The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like. A lower-alkyl group may have a substitution pattern as described earlier in connection with the term  
10 "alkyl".

      The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atom(s), preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Cycloalkyl in which one or more  $-\text{CH}_2-$  group is replaced by O, S, NH and/or N(lower-alkyl) are referred to as "heterocycloalkyl". Examples of heterocycloalkyl groups  
15 are e.g. tetrahydrofuryl, pyrrolidinyl, piperidyl, and morpholinyl.

      The term "alkoxy" refers to the group  $\text{R}'-\text{O}-$ , wherein  $\text{R}'$  is an alkyl. The term "lower-alkoxy" refers to the group  $\text{R}'-\text{O}-$ , wherein  $\text{R}'$  is a lower-alkyl. The term "thio-alkoxy" refers to the group  $\text{R}'-\text{S}-$ , wherein  $\text{R}'$  is an alkyl. The term "thio-lower-alkoxy" refers to the group  $\text{R}'-\text{S}-$ , wherein  $\text{R}'$  is a lower-alkyl.

20       The term "alkenyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 20, preferably up to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkenyl groups as described below also are preferred alkenyl groups. The term "lower-alkenyl" refers to a straight-chain or branched hydrocarbon residue comprising an olefinic bond  
25 and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propenyl. An alkenyl or lower-alkenyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

      The term "alkadienyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising 2 olefinic bonds and up to 20,  
30 preferably up to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkadienyl groups as described below also are preferred alkadienyl groups. The term "lower-alkadienyl" refers to a straight-chain or branched hydrocarbon residue comprising 2 olefinic bonds and up to 7 carbon atoms. An alkadienyl or lower-alkadienyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

35       The term "alkinyl", alone or in combination with other groups, stands for a straight-

chain or branched hydrocarbon residue comprising a triple bond and up to 20, preferably up to 16 carbon atoms. The term "lower-alkinyl" refers to a straight-chain or branched hydrocarbon residue comprising a triple bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propinyl. An alkinyl or lower-alkinyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

The term "alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 20 carbon atoms, preferably 1 to 16 carbon atoms. The term "lower-alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 7, preferably 1 to 6 or 3 to 6 carbon atoms. Straight chain alkylene or lower-alkylene groups are preferred. An alkylene or lower-alkylene group may have a substitution pattern as described earlier in connection with the term "alkyl".

The term "alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 20 carbon atoms, preferably up to 16 carbon atoms. The term "lower-alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 7, preferably up to 5, C-atoms. Straight chain alkenylene or lower-alkenylene groups are preferred. An alkenylene or lower-alkenylene group may have a substitution pattern as described earlier in connection with the term "alkyl".

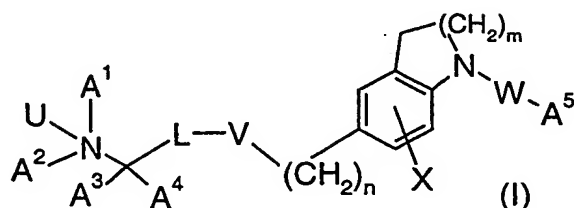
The term "aryl" relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be mono- or multiply-substituted by lower-alkyl, lower-alkinyl, dioxo-lower-alkylene (forming e.g. a benzodioxyl group), halogen, hydroxy, CN, CF<sub>3</sub>, NH<sub>2</sub>, N(H, lower-alkyl), N(lower-alkyl)<sub>2</sub>, aminocarbonyl, carboxy, NO<sub>2</sub>, lower-alkoxy, thio-lower-alkoxy, lower-alkylcarbonyl, lower-alkylcarbonyloxy, lower-alkoxycarbonyl, aryl, and/or aryloxy. Preferred substituents are halogen, CF<sub>3</sub>, NO<sub>2</sub>, CN, lower-alkyl, lower-alkoxy, thio-lower-alkoxy, lower-alkoxycarbonyl, and/or lower-alkylcarbonyl. More preferred substituents are fluorine and chlorine.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur such as furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, or pyrrolyl. The term "heteroaryl" further refers to bicyclic aromatic groups comprising two 5- or 6-membered rings, in which one or both rings can contain 1, 2 or 3 atoms selected from nitrogen, oxygen or sulphur such as e.g. indol or chinolin, or partially hydrogenated bicyclic aromatic groups such as e.g. indolinyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl". Preferred heteroaryl groups are thienyl and pyridyl which can optionally be substituted as described above, preferably with bromine.

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts are formates, 5 hydrochlorides, hydrobromides and methanesulfonic acid salts .

The term "pharmaceutically acceptable esters" embraces esters of the compounds of formula (I), in which hydroxy groups have been converted to the corresponding esters with inorganic or organic acids such as nitric acid, sulphuric acid, phosphoric acid, citric 10 acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms.

In detail, the present invention relates to compounds of formula (I)



wherein

- U is O or a lone pair,
- 5 V is a) O, S, NR<sup>1</sup>, or CH<sub>2</sub>, and L is lower-alkylene or lower-alkenylene,  
b) -CH=CH- or -C≡C-, and L is lower-alkylene or a single bond,
- W is CO, COO, CONR<sup>2</sup>, CSO, CSNR<sup>2</sup>, SO<sub>2</sub>, or SO<sub>2</sub>NR<sup>2</sup>,
- X is hydrogen or one or more optional halogen and/or lower-alkyl substituents,
- m is 1 or 2,
- 10 n is 0 to 7,
- A<sup>1</sup> is hydrogen, lower-alkenyl, or lower-alkyl optionally substituted by hydroxy, lower-alkoxy, or thio-lower-alkoxy,
- A<sup>2</sup> is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower-alkinyl, or lower-alkyl optionally substituted by hydroxy, lower-alkoxy or thio-lower-alkoxy,
- 15 A<sup>3</sup> and A<sup>4</sup> independently from each other are hydrogen or lower-alkyl, or  
A<sup>1</sup> and A<sup>2</sup> or A<sup>1</sup> and A<sup>3</sup> are bonded to each other to form a ring and -A<sup>1</sup>-A<sup>2</sup>- or  
-A<sup>1</sup>-A<sup>3</sup>- are lower-alkylene or lower-alkenylene, optionally substituted by R<sup>3</sup>, in  
which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-A<sup>3</sup>- can optionally be replaced by  
NR<sup>4</sup>, S, or O,
- 20 A<sup>5</sup> is cycloalkyl, cycloalkyl-lower-alkyl, heterocycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, lower-alkyl optionally substituted with hydroxy or lower-alkoxy, alkenyl optionally substituted with hydroxy, or alkadienyl optionally substituted with hydroxy,
- R<sup>3</sup> is hydroxy, lower-alkoxy, thio-lower-alkoxy, N(R<sup>5</sup>, R<sup>6</sup>), or lower-alkyl  
25 optionally substituted by hydroxy,
- R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> independently from each other are hydrogen or lower-alkyl,  
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Preferred are compounds of formula (I) and/or pharmaceutically acceptable salts

thereof. Other preferred embodiments relate to compounds of formula (I) wherein U is a lone pair or to compounds of formula (I) wherein U is O.

Each of the definitions of V given above, a) and b), individually constitutes a preferred embodiment of the present invention. Further, each of the definitions of L,  
5 lower-alkylene, lower-alkenylene and a single bond, individually constitutes a preferred embodiment of the present invention. Compounds as described above in which V is O or CH<sub>2</sub> and L is lower-alkylene or lower-alkenylene relate to a further preferred embodiment of the present invention. Other preferred compounds are those, wherein V is -C≡C- and L is lower-alkylene or a single bond. Compounds as described above, wherein n is 0 also  
10 relate to a preferred embodiment of the present invention. Compounds as described above, in which the number of carbon atoms of L and (CH<sub>2</sub>)<sub>n</sub> together is 10 or less, more preferably 7 or less, are also preferred. The groups of compounds as described above, in which m is 1 or m is 2 individually relate to a preferred embodiment of the present invention.

15 Other preferred compounds of the present invention are those in which A<sup>1</sup> represents lower-alkyl, preferably those in which A<sup>1</sup> is methyl or ethyl. Another group of preferred compounds of the present invention are those in which A<sup>2</sup> represents lower-alkenyl, or lower-alkyl optionally substituted by hydroxy or lower-alkoxy, with those compounds wherein A<sup>2</sup> represents 2-propenyl or 2-hydroxy-ethyl being especially  
20 preferred.

Compounds of formula (I), wherein A<sup>1</sup> and A<sup>2</sup> are bonded to each other to form a ring and -A<sup>1</sup>-A<sup>2</sup>- is lower-alkylene or lower-alkenylene, optionally substituted by R<sup>3</sup>, in which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- can optionally be replaced by NR<sup>4</sup>, S, or O, wherein R<sup>3</sup> and R<sup>4</sup> are as defined above are also preferred. In compounds wherein A<sup>1</sup> and A<sup>2</sup> are  
25 bonded to each other to form a ring, said ring is preferably a 4-, 5-, or 6-membered ring such as e.g. piperidinyl or pyrrolidinyl.

A further preferred embodiment of the present invention relates to compounds of formula (I), wherein A<sup>3</sup> and/or A<sup>4</sup> represent hydrogen.

Compounds of formula (I), wherein A<sup>5</sup> cycloalkyl, cycloalkyl-lower-alkyl,  
30 heterocycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, or lower-alkyl optionally substituted with hydroxy or lower-alkoxy represent a preferred embodiment of the present invention. Other preferred compounds are those in which A<sup>5</sup> is phenyl or benzyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluorine and chlorine, or wherein A<sup>5</sup> is lower-alkyl, with those  
35 compounds wherein A<sup>5</sup> is phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, butyl, or pentyl being

particularly preferred. Another preferred group relates to compounds wherein X is hydrogen. Another preferred group relates to compounds wherein X is fluorine.

Compounds in which  $R^2$  is hydrogen are also preferred. A further preferred embodiment of the present invention relates to those compounds as defined above,  
 5 wherein W is COO, CONR<sup>2</sup>, CSO, or CSNR<sup>2</sup> and R<sup>2</sup> is hydrogen.

Preferred compounds of general formula (I) are those selected from the group consisting of

- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl  
 10 ester,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (2,4-difluoro-phenyl)-amide,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-fluoro-phenyl)-amide,
- 15 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid p-tolylamide,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-bromo-phenyl)-amide,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide,
- 20 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-methoxy-phenyl)-amide,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid naphthalen-2-ylamide,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-acetyl-phenyl)-amide,
- 25 {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(4-bromo-phenyl)-methanone,
- 3-{5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbonyl}-benzonitrile,
- {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-  
 30 methanone,
- {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(5-bromo-thiophen-2-yl)-methanone,
- {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(4-chloro-phenyl)-methanone,
- 35 {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-phenyl-methanone,
- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid (4-chloro-phenyl)-amide,

- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid  
cycloheptylamide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid  
cyclohexylmethyl-amide,  
5 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid 4-chloro-  
benzylamide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid (4-  
trifluoromethyl-phenyl)-amide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid 4-fluoro-  
10 benzylamide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-fluoro-  
phenyl) ester,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-  
phenyl) ester,  
15 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-p-tolyl ester,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-phenyl ester,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid phenylamide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid (4-chloro-phenyl)-  
amide,  
20 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid (2,4-difluoro-  
phenyl)-amide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid (4-fluoro-phenyl)-  
amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl  
25 ester,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (2,4-difluoro-  
phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-fluoro-  
phenyl)-amide,  
30 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid p-tolylamide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-bromo-  
phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (2,4-dimethoxy-  
phenyl)-amide,  
35 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-methoxy-  
phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid naphthalen-2-  
ylamide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-acetyl-



- phenyl)-amide,  
 {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-bromo-phenyl)-  
 methanone,  
 3-{5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbonyl}-benzonitrile,  
 5 {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-  
 methanone,  
 {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(5-bromo-thiophen-2-yl)-  
 methanone,  
 {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-chloro-phenyl)-  
 10 methanone,  
 {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-phenyl-methanone,  
 {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-trifluoromethyl-phenyl)-  
 methanone,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (4-chloro-  
 15 phenyl)-amide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid  
 cycloheptylamide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid  
 cyclohexylmethyl-amide,  
 20 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid 4-chloro-  
 benzylamide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (4-  
 trifluoromethyl-phenyl)-amide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid 4-fluoro-  
 25 benzylamide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid benzylamide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid  
 cyclohexylamide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-  
 30 phenyl) ester,  
 5-{4-[(2-Methoxy-ethyl)-methyl-amino]-butoxy}-2,3-dihydro-indole-1-carbothioic acid  
 O-(4-chloro-phenyl) ester,  
 5-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-2,3-dihydro-indole-1-carbothioic acid O-  
 (4-chloro-phenyl) ester,  
 35 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid O-(4-fluoro-  
 phenyl) ester,  
 Allyl-{5-[1-(4-chloro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-pentyl}-methyl-  
 amine,  
 Allyl-{5-[1-(4-bromo-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-pentyl}-methyl-

- amine,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
4-chloro-phenyl ester,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
5 tert-butyl ester,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
ethyl ester,
- Allyl-{4-[1-(4-chloro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-but-2-enyl}-  
methyl-amine,
- 10 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-  
butyl ester,
- Allyl-{5-[1-(4-chloro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pentyl}-  
methyl-amine,
- 6-[3-(Allyl-methyl-amino)-propoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
15 chloro-phenyl ester,
- 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
chloro-phenyl ester,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-methoxy-phenyl)-amide,
- 20 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
p-tolylamide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
naphthalen-1-ylamide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
25 (2,4-difluoro-phenyl)-amide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-fluoro-3-trifluoromethyl-phenyl)-amide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-fluoro-phenyl)-amide,
- 30 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(2,4-dimethoxy-phenyl)-amide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-methylsulfanyl-phenyl)-amide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
35 (4-bromo-phenyl)-amide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
benzylamide,
- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-butyl-phenyl)-amide,

- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-acetyl-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
chloro-phenyl ester.
- 5 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
chloro-phenyl ester,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-  
tolylamide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-  
10 fluoro-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-  
bromo-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-  
butyl-phenyl)-amide,
- 15 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
bromo-phenyl ester,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
fluoro-phenyl ester,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolyl  
20 ester,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid hexyl  
ester,  
3-{6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carbonyl}-  
benzonitrile,
- 25 {6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-bromo-  
phenyl)-methanone,  
{6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(5-bromo-  
thiophen-2-yl)-methanone,  
{6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-  
30 methanone,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
methoxy-phenyl ester,  
3-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carbonyl}-  
benzonitrile,
- 35 {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-bromo-  
phenyl)-methanone,  
1-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-2-(2,4-  
difluoro-phenyl)-ethanone,  
1-(4-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carbonyl})-

- phenyl)-ethanone,  
{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(5-bromo-  
thiophen-2-yl)-methanone,  
{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(3-chloro-  
5 phenyl)-methanone,  
1-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-2-(4-  
fluoro-phenyl)-ethanone,  
{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-  
phenyl)-methanone,  
10 {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-chloro-  
phenyl)-methanone,  
{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-  
trifluoromethyl-phenyl)-methanone,  
{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-pyridin-3-yl-  
15 methanone,  
{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-3-  
methyl-phenyl)-methanone,  
6-[4-(allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-  
nitro-phenyl ester,  
20 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
hexyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
4-bromo-phenyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
25 isobutyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
phenyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
4-methoxy-phenyl ester,  
30 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
p-tolyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
4-methoxycarbonyl-phenyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
35 butyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
4-fluoro-phenyl ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
phenethyl-amide,

- 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester,  
 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester,  
 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-bromo-phenyl  
 5 ester,  
 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid hexyl ester,  
 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluoro-phenyl)-amide,  
 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolylamide,  
 10 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-bromo-phenyl)-amide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (2,4-difluoro-phenyl)-amide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-  
 15 fluoro-phenyl)-amide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolylamide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-bromo-phenyl)-amide,  
 20 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-methoxy-phenyl)-amide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
 25 naphthalen-2-ylamide,  
 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-acetyl-phenyl)-amide,  
 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-fluoro-phenyl ester,  
 30 {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-bromo-phenyl)-methanone,  
 3-{6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbonyl}-benzonitrile,  
 {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-  
 35 methanone,  
 {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(5-bromo-thiophen-2-yl)-methanone,  
 {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-chloro-phenyl)-methanone,

- {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-phenyl-methanone,  
{6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-trifluoromethyl-phenyl)-methanone,  
(4-Bromo-phenyl)-[6-(4-diethylamino-butoxy)-3,4-dihydro-2H-quinolin-1-yl]-  
5 methanone,  
3-[6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carbonyl]-benzonitrile,  
[6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinolin-1-yl]-(4-fluoro-phenyl)-  
methanone,  
(5-Bromo-thiophen-2-yl)-[6-(4-diethylamino-butoxy)-3,4-dihydro-2H-quinolin-1-yl]-  
10 methanone,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid (4-chloro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid  
cycloheptylamide,  
15 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid  
cyclohexylmethyl-amide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid 4-chloro-benzylamide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid (4-trifluoromethyl-phenyl)-amide,  
20 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid 4-fluoro-benzylamide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid  
benzylamide,  
25 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid  
cyclohexylamide,  
6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-fluoro-phenyl) ester,  
6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-chloro-phenyl) ester,  
30 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-fluoro-phenyl) ester,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-chloro-phenyl) ester,  
35 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid O-phenyl ester,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid  
phenylamide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-

- phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluoro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-fluoro-phenyl)-amide,  
5 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-chloro-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid p-tolylamide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-cyano-phenyl)-amide,  
10 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-methoxy-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (3,4-difluoro-phenyl)-amide,  
15 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (3-fluoro-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (2,4-difluoro-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (2,5-difluoro-phenyl)-amide,  
20 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-bromo-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid phenylamide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (3-methyl-butyl)-amide,  
25 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (furan-2-ylmethyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid ethylamide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid butylamide,  
30 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (2-methyl-butyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (2-methoxy-ethyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (4-butyl-phenyl)-amide,  
35 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (tetrahydro-furan-2-ylmethyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-phenyl)-amide,

- 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-fluoro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-bromo-phenyl)-amide,  
5 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (p-tolyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3,4-difluoro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-  
10 trifluoromethyl-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3-fluoro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-cyano-phenyl)-amide,  
15 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluoro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-methoxy-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid  
20 (2,5-difluoro-phenyl)-amide,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-phenyl)-amide,  
25 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-cyano-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3-fluoro-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-  
30 bromo-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-methoxy-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluoro-phenyl)-amide,  
35 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid p-tolylamide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-fluoro-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,5-



- difluoro-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide,  
6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3,4-difluoro-phenyl)-amide,  
5 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid (4-chloro-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-cyano-phenyl)-amide,  
10 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid cycloheptylamide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-methoxy-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-phenyl)-amide,  
15 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2, 5-difluoro-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-bromo-phenyl)-amide,  
20 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2, 4-difluoro-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid p-tolylamide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid  
25 butylamide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3-fluoro-phenyl)-amide,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid phenylamide,  
30 5-[4-(Allyl-methyl-amino)-but-2-enyloxy]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester,  
5-{4-[(2-Methoxy-ethyl)-methyl-amino]-butoxy}-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester,  
35 5-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester,  
6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester,  
6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-

butyl ester,

6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester,  
and

6-[5-(Allyl-methyl-amino)-pentyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl  
5 ester

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Further preferred compounds of general formula (I) are those selected from the  
group consisting of

5-[5-(Allyl-methyl-amino)-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-  
10 chloro-phenyl ester,

6-Fluoro-5-{5-[(2-hydroxy-ethyl)-methyl-amino]-pent-1-ynyl}-2,3-dihydro-indole-1-  
carboxylic acid 4-chloro-phenyl ester,

5-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pent-1-ynyl}-6-fluoro-2,3-dihydro-indole-1-  
carboxylic acid 4-chloro-phenyl ester,

15 2-({5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-ynyl}-methyl-  
amino)-ethanol,

2-(Ethyl-{5-[6-fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-ynyl}-  
amino)-ethanol,

6-Fluoro-5-[5-(methyl-propyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid  
20 phenyl ester,

2-({5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pentyl}-methyl-  
amino)-ethanol,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Particularly preferred compounds of general formula (I) are those selected from the  
25 group consisting of

5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-  
phenyl) ester,

5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-  
phenyl) ester,

30 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl  
ester,

6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid  
(4-fluoro-phenyl)-amide,

5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid 4-fluoro-  
35 benzylamide,

5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid 4-chloro-  
benzylamide,

- 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-fluoro-phenyl)-amide,  
 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-fluoro-phenyl) ester,  
 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid (4-chloro-phenyl)-amide,  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (2-methyl-butyl)-amide, and  
 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid butylamide,  
 and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

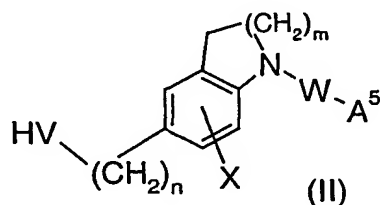
- Further particularly preferred compounds of general formula (I) are those selected from the group consisting of  
 5-[5-(Allyl-methyl-amino)-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester,  
 5-[5-[Ethyl-(2-hydroxy-ethyl)-amino]-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester,  
 6-Fluoro-5-[5-(methyl-propyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid phenyl ester,  
 and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

- Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers or as racemats. The invention embraces all of these forms.

- It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

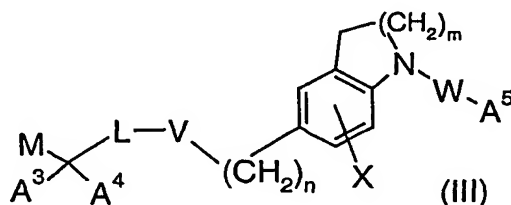
The present invention also relates to a process for the manufacture of compounds as described above, which process comprises

- a) reacting a compound of formula (II)



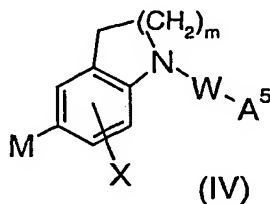
with a compound  $(A^1, A^2, U)N-C(A^3, A^4)-L-M$ , wherein V is O, S or  $NR^1$ , M is mesylate, tosylate, triflate, Cl, Br or I, and U,  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , L, W, X, m, n and  $R^1$  are as defined above, or wherein HV is mesylate, tosylate, triflate, Cl, Br or I, and M is OH, SH or  $NHR^1$ , and  $R^1$  is as defined above,

5 or b) reacting a compound of formula (III)



with a compound  $NHA^1, A^2$ , wherein M is mesylate, tosylate, triflate, Cl, Br or I, and  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , L, V, W, X, m and n are as defined above,

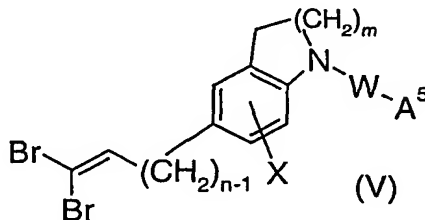
or c) reacting a compound of formula (IV)



10

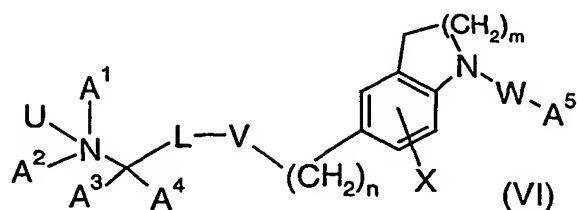
with a compound  $(A^1, A^2, U)N-C(A^3, A^4)-L-C\equiv CH$ , wherein M is Br or  $F_3CO_2SO$ , and U,  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , L, W, X and m are as defined above,

or d) reacting a compound of formula (V)



15 with a compound  $(A^1, A^2, U)N-C(A^3, A^4)-L-M$ , wherein M is mesylate, tosylate, triflate, Cl, Br or I, and  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , W, U, L, X, m and n are as defined above,

or e) hydrogenating a compound of formula (VI)



wherein V is  $-C\equiv C-$ , and  $A^1, A^2, A^3, A^4, A^5, U, W, L, X, m$  and  $n$  are as defined above,

and optionally converting a compound according to any of claims 1 to 21 to a pharmaceutically acceptable salt,

- 5 and optionally converting a compound according to any of claims 1 to 21, wherein U is a lone pair, to a corresponding compound wherein U is O.

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

- As described above, the compounds of formula (I) of the present invention can be used for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections and gallstones, and/or treatment and/or prophylaxis of impaired glucose tolerance, diabetes, tumors and/or hyperproliferative disorders, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia.
- 15 Hyperproliferative skin and vascular disorders particularly come into consideration as hyperproliferative disorders.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

- Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia.
- 20  
25

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of

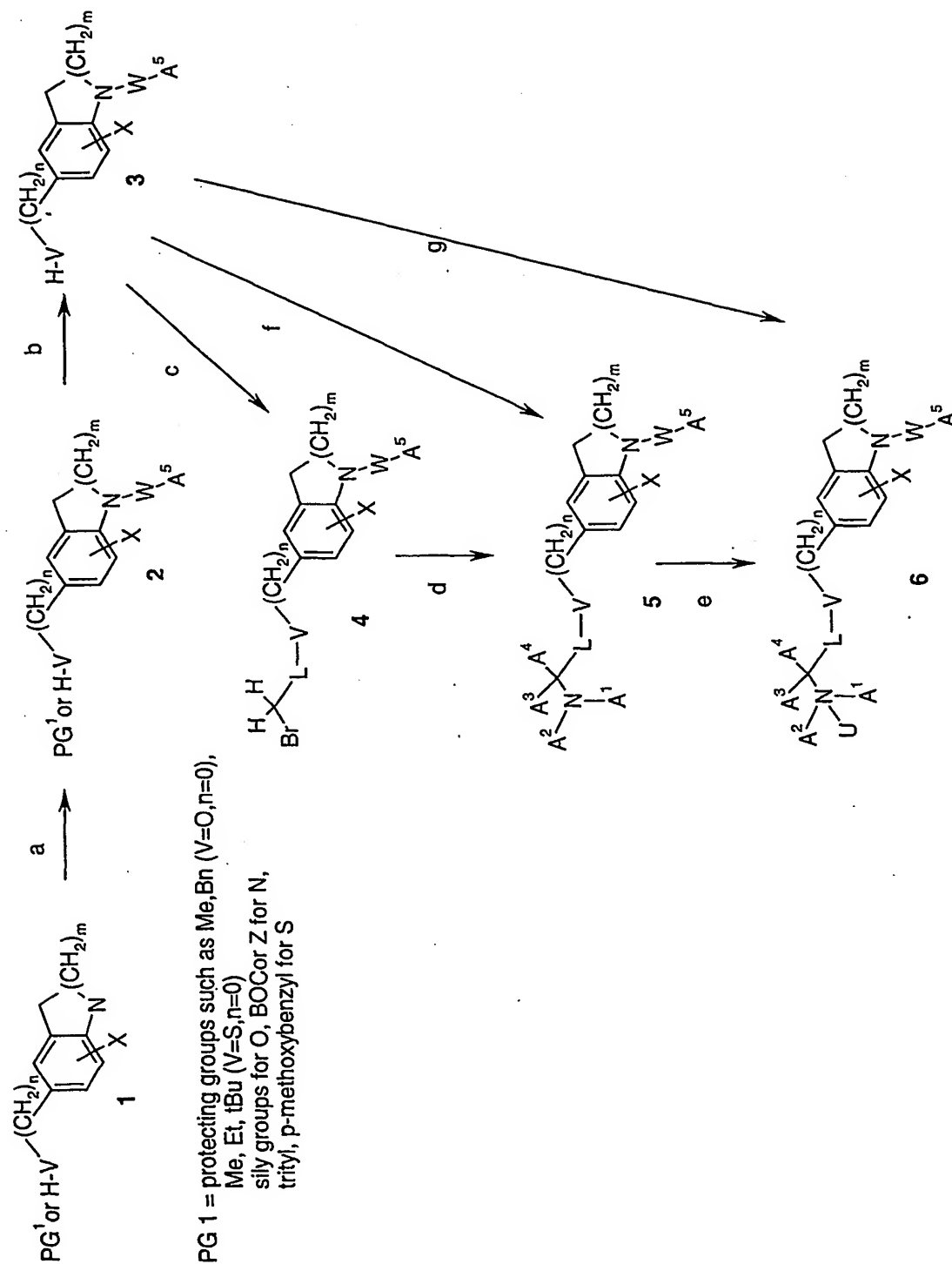
impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia, which method comprises administering a compound as defined above to a human being or animal.

The invention further relates to the use of compounds as defined above for the  
5 treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia.

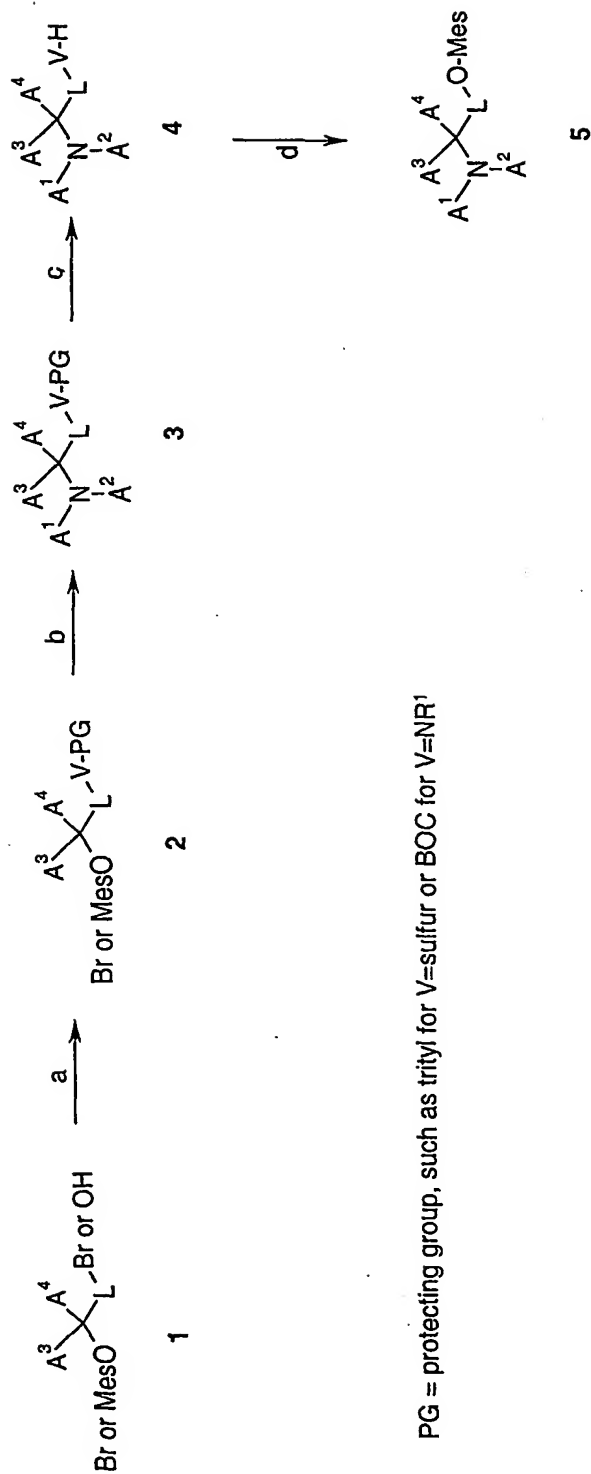
10 In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and  
15 diabetes, preferably for the treatment and/or prophylaxis of hypercholesterolemia and/or hyperlipemia. Such medicaments comprise a compound as defined above.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art.  
20 Starting materials are either commercially available or can be prepared by methods analogous to the methods given below or in the examples or by methods known in the art, e.g. by methods described in: Richard J. Sundberg Indoles (Best Synthetic Methods), Series Editor A.R. Katritzky, O. Meth-Cohn, C. W. Rees, Academic Press, San Diego 1996, or in Houben-Weyl Methoden der Organischen Chemie, R.P. Kreker, Ed., Georg Thieme  
25 Verlag, Stuttgart, 1994, or The Chemistry of Heterocyclic Compounds. A Series of Monographs, Vol. 32, Quinolines. Part 1-3, Weissenberger, E.C. Taylor, G. Jones, Eds, Wiley, London.

Scheme 1



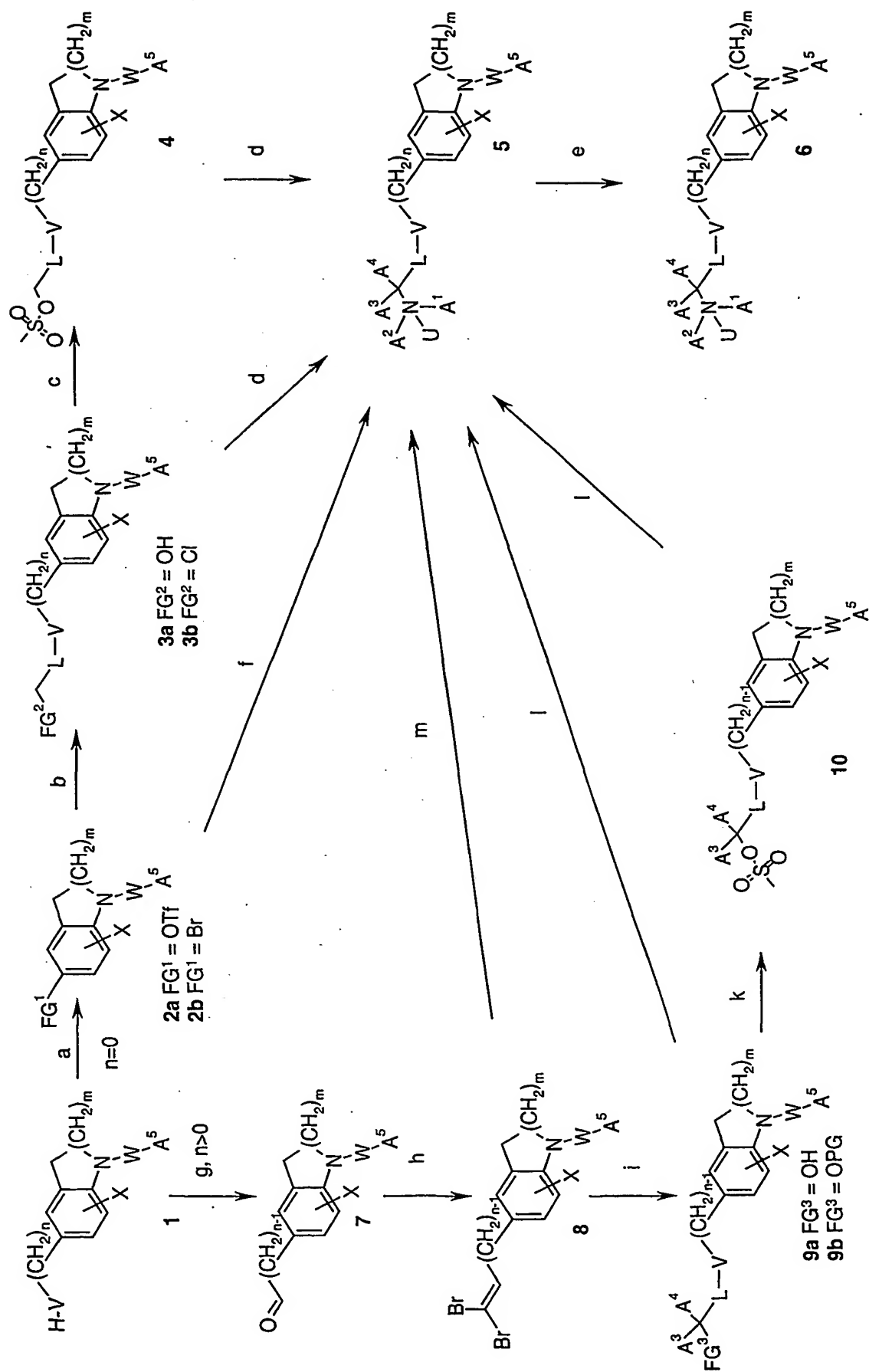
- 27 -

Scheme 2

PG = protecting group, such as trityl for V=sulfur or BOC for V=NR'



Scheme 3



## Scheme 1

If starting material 1 is a tetrahydroquinoline derivative ( $m=2$ ), it may be derived from the corresponding quinoline derivative by hydrogenation with  $\text{PtO}_2$  in a suitable solvent such as methanol, ethanol. If starting material 1 is an indoline derivative ( $m=1$ ), it may be derived from the corresponding indole derivative for example by treatment with  $\text{NaCNBH}_3$  in acetic acid or trifluoro acetic acid or by employing other methods known in the art.

Derivative 1 is either N-protected (e.g.  $(\text{BOC})_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ) to yield compound 2 or is directly converted to the desired  $\text{A}^5\text{W}$ -substituted derivative 2 using one of the methods described later for compound 5.

Deprotection of the V-group can be achieved, if 2 is a 5-benzyloxyindoline derivative, by hydrogenation with e.g.  $\text{Pd/C}$  in solvents like methanol, ethanol or ethyl acetate, if 2 is a 5-methoxy-indoline derivative, by treatment for example with lithium-tri-sec-butylborohydride in THF. For  $\text{V}=\text{S}$ ,  $\text{NR}^1$  or  $\text{V}=\text{O}$  and  $n>0$ , deprotection using procedures known in the art (step c) yields the building block 3.

Alkylation of the phenol/thiophenol 3 ( $\text{V}=\text{O}$ ,  $\text{S}$ ,  $n=0$ ) is accomplished in acetone or DMF with  $\text{K}_2\text{CO}_3$  and a suitable dihaloalkane or dihaloalkene (halogene is here represented by bromine, but can also be chlorine or iodine. It is also possible to use mesylates, tosylates or triflates instead of halogenides) at reflux to yield halogenide 4 (step c). For the preparation of derivatives 4 ( $\text{V}=\text{O}$ ,  $n>0$ ), the alcohol 3 can be treated with  $\alpha,\omega$ -dihaloalkanes or  $\alpha,\omega$ -dihaloalkenes under phase transfer conditions e.g.  $\alpha,\omega$ -dihaloalkanes/dihaloalkenes,  $\text{NaOH}$ ,  $n\text{Bu}_4\text{NHSO}_4$ . For  $\text{V}=\text{S}$ ,  $\text{O}$  or  $\text{NR}^1$ , the derivative 3 may be treated with  $\alpha,\omega$ -dihaloalkane in the presence of  $\text{NaH}$  in DMF  $0^\circ\text{C}$  to RT to yield bromide 4. For shorter alkanes (methyl, ethyl), the method of choice is the in situ generation of the haloalkane-triflate (from the corresponding haloalkanol with trifluoromethanesulfonic anhydride/2,6-di-tert-butylpyridine in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ ). This haloalkane-triflate may then be reacted with 3 in the presence of a base such as 2,6-di-tert-butylpyridine in nitromethane at  $60^\circ\text{C}$  to yield bromide 4 [analogously to a procedure of Belostotskii, Anatoly M.; Hassner, Alfred. Synthetic methods. 41. Etherification of hydroxysteroids via triflates. Tetrahedron Lett. (1994), 35(28), 5075].

Compound 4 can be converted to the amine 5 with an excess of the corresponding amine  $\text{NHA}^1\text{A}^2$  in a suitable solvent such as DMA, DMF, MeOH at RT or at  $50\text{--}65^\circ\text{C}$  or by treatment with  $\text{NHA}^1\text{A}^2$ ,  $\text{NaH}$  in solvents such as DMF or THF (step d).

Compound 5 can be N-deprotected using TFA in  $\text{CH}_2\text{Cl}_2$  for BOC-groups or by hydrogenation in methanol, ethanol or ethyl acetate with  $\text{Pd/C}$  for Z-groups.

The resulting amine (not shown in scheme 1) may be treated according to one of the following procedures to yield the appropriate A<sup>5</sup>W-substituted derivative 5 (separation by HPLC was necessary in some cases).

- 5 a) Sulfonamides: Sulfonylation of the amines is done in dioxane or CH<sub>2</sub>Cl<sub>2</sub> with Huenig's base and a sulfonyl chloride over night at RT to yield the sulfonamide 5.
- b) Carbamates: The amines may be reacted with A<sup>5</sup>OCOCl/Huenig's base or pyridine in dioxane, THF, DMF or CH<sub>2</sub>Cl<sub>2</sub>. Alternatively, the chloroformates may be prepared in situ by treatment of A<sup>5</sup>OH with Cl<sub>3</sub>COCl in the presence of quinoline followed by reaction with the amines in the presence of Huenig's base.
- 10 c) Thiocarbamates: The amines may be reacted with A<sup>5</sup>OCSCl in dioxane.
- d) Ureas: The amines may be reacted with isocyanate in dioxane at room temperature.
- e) Thioureas: The amines may be reacted with isothiocyanate in dioxane at room temperature.
- 15 f) Amides: The amines may be reacted with A<sup>5</sup>COOH/EDCI/DMAP (with anhydride formation, and subsequent addition of the starting amine at -10°C to room temperature) or alternatively with A<sup>5</sup>COOH/EDCI/DMAP or A<sup>5</sup>COOH/Huenig's base/EDCI/HOBT in DMF, dioxane or CH<sub>2</sub>Cl<sub>2</sub> at room temperature.
- 20 g) Sulfamides: The amines may be reacted with sulfamoyl chlorides in dioxane in the presence of an excess of triethylamine to yield sulfamide 5. The sulfamoyl chlorides can be prepared from A<sup>5</sup>NH<sub>2</sub> and chlorosulfonic acid in CH<sub>2</sub>Cl<sub>2</sub> at 0°C to room temperature followed by reaction with PCl<sub>5</sub> in toluene at 75°C. Alternatively, the sulfamoyl chlorides can be synthesized in acetonitrile with A<sup>5</sup>NH<sub>2</sub> and sulfuryl chloride at 0°C to 65°C.

25 Alternatively, the compound 3 may be converted to the amine 5 by attaching the pre-assembled fragment A<sup>1</sup>A<sup>2</sup>NC(A<sup>3</sup>A<sup>4</sup>)LV-OMes/halogenide/triflates, which can be synthesised by known methods (shown e.g. in Scheme 2), using alkylating conditions (step f). Compounds 3 (V=O, n>0) can also be mesylated (V=OMes) and then reacted with A<sup>1</sup>A<sup>2</sup>NC(A<sup>3</sup>A<sup>4</sup>)L-VH (synthesis as described in Scheme 2) in e.g. DMF with NaH as base to yield 5 (with V=O, S, NR<sup>1</sup>).

30 Amine 5 may be converted to a salt or to the N-oxide 6 (step e). For N-oxide 6 (V=O) a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH<sub>2</sub>Cl<sub>2</sub> at

RT may be used. For the preparation of the N-oxides 6 ( $V=S$  or  $NR^1$ ) an alternative route has to be employed (step g): Oxidation of the pre-assembled fragment  $A^1A^2NC(A^3A^4)L$  - OMe/halogenide to the corresponding N-oxide derivative, followed by alkylation of the compound 3 to give compound 6 directly.

- 5        If  $WA^5$  is a protective group, this may be cleaved as described for derivative 5 and the final moieties  $WA^5$  may be introduced as described above.

#### Scheme 2

Scheme 2 shows the synthesis of amino-VH sidechain 4 that may be used for the synthesis of compounds with the corresponding V-spacers ( $V=NR^1$ , S, or O).  $\alpha,\omega$ -  
10    dihaloalkane, mesyl-alkanyl-halogenide,  $\alpha,\omega$ -dihaloalkene, mesyl-alkenyl-halogenide 1 may be treated with a suitable protected amine ( $HNR^1$ -PG, PG=protecting group, e.g. BOC) in DMA or a thiol (HS-PG e.g., triphenylmethanethiol) in the presence of NaH in DMA to yield the compound 2 (step a). Treatment with the amine  $A^1A^2NH$  yields the S- or N-protected amine 3 (step b) or in the case of  $\alpha,\omega$ -haloalkanol or  $\alpha,\omega$ -haloalkenol 1  
15    directly amino-alcohol 4. N-deprotection with procedures known in the art e.g. TFA in  $CH_2Cl_2$  yields the amine side chain 4 (step c). The deprotection of the thiol moiety in 3 may be achieved with TFA/triisopropylsilane in  $CH_2Cl_2$  at 0 °C to RT to yield the aminothiol 4 (step c). Aminoalkanol 4 can be transformed further to mesylate 5 (step d).

#### Scheme 3

20        In Scheme 3, the preparation of compounds of formula 6, in which V represents  $-CH_2-$ ,  $-CH=CH-$  or  $-C\equiv C-$  is outlined. The starting material is derivative 1, which may be converted to the triflate 2a in pyridine with trifluoromethanesulfonic anhydride at 0 °C to RT (step a). Sonogashira-coupling (step b) of the triflate 2a and a suitable alkynol or alkynenechloride in piperidine with  $Pd(PPh_3)_4/CuI$  at 45 °C to 80 °C in analogy to a  
25    literature procedure yields alcohol 3a or chloride 3b [Stara, Irena G.; Stary, Ivo; Kollarovic, Adrian; Teply, Filip; Saman, David; Fiedler, Pavel. Coupling reactions of halobenzenes with alkynes. The synthesis of phenylacetylenes and symmetrical or unsymmetrical 1,2-diphenylacetylenes. Collect. Czech. Chem. Commun. (1999), 64(4), 649-672.].

30        Alternatively, the alkynes 3a or 3b can be prepared by Sonogashira reaction of the bromo-derivatives 2b with the corresponding alkynols or alkynenechlorides.

Mesylation of alcohol 3a with methanesulfonylchloride e.g. in solvents such as pyridine or  $CH_2Cl_2$  with bases like triethylamine or Huenig's base optionally in the presence of DMAP (reaction step c) and subsequent amination (reaction step d) of the resulting mesylate 4 with a suitable amine  $NHA^1A^2$  in a solvent like DMA, DMF or MeOH

at RT or at 50-65° yields the amine 5. Alcohol 3a can also be treated with trifluoromethane sulfonic acid anhydride and Huenig's base at -15 °C in CH<sub>2</sub>Cl<sub>2</sub> (in situ generation of the corresponding triflate) followed by treatment with the corresponding amine NHA<sup>1</sup>A<sup>2</sup> at -15°C to RT. This is especially the method of choice for but-3-yn-1-ol-derivatives 3a.

- 5 Chloride 3b can be transformed directly or via iodide (Finkelstein reaction) to the amine 5, as described above (step d). Compounds 5 in which V is -CH<sub>2</sub>- or -CH=CH- can be obtained by hydrogenation of compound 5 in solvents like MeOH or EtOH with Pt<sub>2</sub>O·H<sub>2</sub>O or Pd/C (yields the saturated analogue 5) or by selective hydrogenation with other known methods (e.g. Lindlar or DIBAH, REDAL) (yields the double bond analogue 10 5). Optionally, the hydrogenation described above can be performed at an earlier stage e.g. the alcohol 3a or mesylate 4.

Alternatively, the group A<sup>1</sup>A<sup>2</sup>NC(A<sup>3</sup>A<sup>4</sup>C)-L-acetylene can be synthesised by known methods and attached to compound 2a or 2b (Sonogashira-coupling), to yield the compounds of the present invention 5 (reaction step f).

- 15 Compounds of the formula 5 (n>0) may be synthesised by Swern oxidation of the alcohol 1 (V=O and n>0) to yield the corresponding aldehyde 7 (step g) as an intermediate. The aldehyde 7 may be treated with triphenylphosphine, tetra-bromo-methane and triethylamine in CH<sub>2</sub>Cl<sub>2</sub> at 0°C to RT to yield 2,2-Dibromo-vinyl derivative 8 (step h). Rearrangement with n-BuLi (ca 1.6 M in hexane) in THF at -78°C, followed by 20 reaction with formaldehyde (-78°C to RT) leads to the propargyl alcohol 9a (step i, side chain extension through application of the Corey-Fuchs method), following conditions described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org. Chem. (1996), 61(17), 5729-5735; and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. 25 Synthesis of talaromycins A, B, C, and E. J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.

- For longer side chains, the rearrangement is performed with n-BuLi (ca 1.6 M in hexane) in THF at -78°C as above, followed by addition of a co-solvens such as DMPU and reaction with O-protected 1-bromo-alcohols (e.g. 1-bromo-n-tetrahydro- 30 pyrananyloxyalkane) to yield the O-protected compounds 9b (step i). O-protected compounds 9b can be deprotected to the corresponding alkynol 9a (in MeOH at 50-60°C, in the presence of catalytic amount of pyridinium toluene-4-sulfonate). Alcohol 9a can be reacted with Huenig's base/trifluoromethane sulfonic acid anhydride at -15°C in CH<sub>2</sub>Cl<sub>2</sub> (in situ generation of the corresponding triflate) followed by treatment with Huenig's base 35 and the corresponding amine NHA<sup>1</sup>A<sup>2</sup> at -15°C to RT to yield amine 5. Alternatively, mesylation of alcohol 9a with methanesulfonylchloride, pyridine and DMAP in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C to RT yields mesylate 10. Conversion of the mesylate 10 to the amine 5 can be

accomplished with an excess of the corresponding amine  $\text{NHA}^1\text{A}^2$  in DMA at RT or as described above (step l).

Compounds 5 in which V is  $-\text{CH}_2-$  or  $-\text{CH}=\text{CH}-$  can be obtained by hydrogenation of compound 5 itself or the intermediates 9a, 9b or 10. The hydrogenation may be performed in EtOH or MeOH with  $\text{Pt}_2\text{O} \cdot \text{H}_2\text{O}$  or Pd/C (yields the saturated analogues 5, 9a, 9b, or 10) or by selective hydrogenation to obtain the double bond by other known methods (e.g. Lindlar or DIBAH, REDAL) and transforming the intermediates afterwards to 5.

Alternatively, for the introduction of the group  $\text{A}^1\text{A}^2\text{N}(\text{A}^3\text{A}^4\text{C})\text{L}$  in which  $\text{A}^3$  and/or  $\text{A}^4$  are not H, the following steps have to be performed starting from compound 8 (step m or steps i and l): for L = lower alkanes, the building block  $\text{A}^1\text{A}^2\text{N}(\text{A}^3\text{A}^4\text{C})\text{L}$ -halogenide/mesylate is synthesised by known methods (or in analogy to the methods described in Scheme 2) and introduced (step m) under the same condition as described above for step i. For L = single bond, the introduction of the group  $\text{A}^1\text{A}^2\text{N}(\text{A}^3\text{A}^4\text{C})$  with  $\text{A}^3$  and/or  $\text{A}^4$  not H, a two step procedure has to be followed: first the rearrangement of 8 with n-BuLi (ca 1.6 M in hexane) in THF at  $-78^\circ\text{C}$ , followed by reaction with the corresponding aldehyde ( $\text{A}^3$  or  $\text{A}^4\text{-COH}$ ) or ketone ( $\text{A}^3\text{COA}^4$ , at  $-78^\circ\text{C}$  to RT) leads to the  $\text{A}^3\text{A}^4$  substituted propargyl alcohol 9a (step i) which is e.g. mesylated or transformed to a phosphorester or a chloride (not shown) and reacted with the desired  $\text{A}^1\text{A}^2$ -substituted-amine in the presence of Tetrakis(triphenylphosphine)palladium (for the phosphorester) or Cu(I)Cl/Cu bronze and Huenig's base (for the chloride) to yield the desired  $\text{A}^3, \text{A}^4$ -substituted compound 5 (step l). (see: Bartlett, Paul A.; McQuaid, Loretta A.. Total synthesis of ( $\pm$ )-methyl shikimate and ( $\pm$ )-3-phosphoshikimic acid. J. Am. Chem. Soc. (1984), 106(25), 7854-60 and Cooper, Matthew A.; Lucas, Mathew A.; Taylor, Joanne M.; Ward, A. David; Williamson, Natalie M. A convenient method for the aromatic amino-Claisen rearrangement of N-(1,1-disubstituted-allyl)anilines. Synthesis (2001), (4), 621-625.)

Amine 5 may be converted to a salt or to the N-oxide 6 using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in  $\text{CH}_2\text{Cl}_2$  at RT (step e).

If  $\text{WA}^5$  is a protecting group, this may be cleaved and the final moieties  $\text{WA}^5$  may be introduced as described for derivative 5 in scheme 1.

The following tests were carried out in order to determine the activity of the compounds of formula I and their salts.

Inhibition of human liver microsomal 2,3-oxidosqualene-lanosterol cyclase (OSC)

Liver microsomes from a healthy volunteer were prepared in sodium phosphate  
5 buffer (pH 7.4). The OSC activity was measured in the same buffer, which also contained  
1mM EDTA and 1mM dithiothreitol. The microsomes were diluted to 0.8mg/ml protein  
in cold phosphate buffer. Dry [ $^{14}$ C]R,S-monooxidosqualene (MOS, 12.8 mCi/mmol) was  
diluted to 20 nCi/ $\mu$ l with ethanol and mixed with phosphate buffer-1% BSA (bovine  
serum albumin). A stock solution of 1 mM test substance in DMSO was diluted to the  
10 desired concentration with phosphate buffer-1% BSA. 40  $\mu$ l of microsomes were mixed  
with 20  $\mu$ l of the solution of the test substance and the reaction was subsequently started  
with 20  $\mu$ l of the [ $^{14}$ C]R,S-MOS solution. The final conditions were: 0.4mg/ml of  
microsomal proteins and 30  $\mu$ l of [ $^{14}$ C]R,S-MOS in phosphate buffer, pH 7.4, containing  
0.5% albumin, DMSO <0.1% and ethanol <2%, in a total volume of 80  $\mu$ l.

15 After 1 hour at 37°C the reaction was stopped by the addition of 0.6 ml of 10%  
KOH-methanol, 0.7ml of water and 0.1ml of hexane:ether (1:1, v/v) which contained 25  $\mu$ g  
of non-radioactive MOS and 25  $\mu$ g of lanosterol as carriers. After shaking, 1 ml of  
hexane:ether (1:1, v/v) was added to each test tube, these were again shaken and then  
centrifuged. The upper phase was transferred into a glass test tube, the lower phase was  
20 again extracted with hexane:ether and combined with the first extract. The entire extract  
was evaporated to dryness with nitrogen, the residue was suspended in 50  $\mu$ l of  
hexane:ether and applied to a silica gel plate. Chromatographic separation was effected in  
hexane:ether (1:1, v/v) as the eluent. The R<sub>f</sub> values for the MOS substrate and the  
lanosterol product were 0.91 and, respectively, 0.54. After drying, radioactive MOS and  
25 lanosterol were observed on the silica gel plate. The ratio of MOS to lanosterol was  
determined from the radioactive bands in order to determine the yield of the reaction and  
OSC inhibition.

The test was carried out on the one hand with a constant test substance  
concentration of 100nM and the percentage OSC inhibition against controls was  
30 calculated. The more preferred compounds of the present invention exhibit inhibitions  
larger than 50%. In addition, the test was carried out with different test substance  
concentrations and subsequently the IC<sub>50</sub> value was calculated, i.e. the concentration  
required to reduce the conversion of MOS into lanosterol to 50% of the control value. The  
preferred compounds of the present invention exhibit IC<sub>50</sub> values of 1 nM to 10  $\mu$ M,  
35 preferrably of 1 - 100 nM.

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration for the prevention and



control of topical and systemic infections by pathogenic fungi. For cholesterol lowering and treatment of impaired glucose tolerance and diabetes the daily dosage conveniently amounts to between 1 and 1000mg, preferably 5 to 200mg, for adult patients. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

- 5       The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 5-200 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

## Abbreviations:

AcOH= acetic acid, n-BuLi = n-Butyl lithium, CuI = copper iodide, DMF = N,N-dimethylformamide, Et<sub>2</sub>O = ether = diethyl ether, EtOAc = ethyl acetate, eq. = equivalents,  
5 Huenig's base = N,N-diisopropylethylamine, KOtBu = potassium tert. butylate, MeOH = methanol, NaOtBu = sodium tert. butylate, NEt<sub>3</sub> = triethylamine, Pd/C = palladium on carbon, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> = bis(triphenylphosphine)palladium(II) chloride, Pd(Ph<sub>3</sub>P)<sub>4</sub> = tetrakis(triphenylphosphine)palladium, RT = room temperature, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

## 10 General remarks

All reactions were performed under argon.

The purification of the final amines by preparative HPLC [e.g. RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile] yielded mixtures of the corresponding amino formate and the corresponding halogenide or methanesulfonic acid  
15 salt which was used in the reaction. The ratio was not always determined, the purity of the final amino salts was >80% after LC-MS.

### Example 1

#### 1.1

1,2,3,4-Tetrahydro-quinolin-6-ol can be prepared from quinolin-6-ol according to Moore; Capaldi; J.Org.Chem., 29, 1964, 2860 or Hoenel, Michael; Vierhapper, Friedrich W.; J.Chem.Soc.Perkin Trans.1, 1980, 1933-1939.

#### 1.2

To 750 mg (5 mmol) 1,2,3,4-Tetrahydro-quinolin-6-ol in 10 ml THF 950 mg (5 mmol) 4-chlorophenylchloroformate were added. The solution was stirred at RT for 30 min, 0.5 ml (6 mmol) pyridine were added and the solution was stirred for additional 30 min. The mixture was concentrated in vacuo and dissolved in EtOAc, water and 2M HCl was added. The inorganic phase was extracted with EtOAc, the combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 49:1 yielded 600 mg (40%) 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless gum, MS: 303 (M, 1Cl).

#### 1.3

To 304 mg (1 mmol) 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester in 4 ml DMF 420 mg (3 mmol) K<sub>2</sub>CO<sub>3</sub> (powdered) and 416 mg (2 mmol) 1,4-dibromobutene were added. The mixture was stirred at 50°C for 1h, diluted with EtOAc and water. 2M HCl was added and the inorganic phase was extracted with EtOAc. The combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by column chromatography on silica gel with hexane/EtOAc 9:1 to 4:1 to yield 250 mg (46%) 6-(4-Bromo-but-2-enyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless gum, MS: 436 (MH<sup>+</sup>, 1Br, 1Cl).

#### 1.4

To 245 mg (0.8mmol) 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester in 5 ml acetone 323 mg (2.3 mmol) K<sub>2</sub>CO<sub>3</sub> (powdered) and 0.21 ml (2.1 mmol) 1,3-dibromopropane were added. The mixture was stirred at reflux for 4h, filtered and concentrated. The residue was dissolved in EtOAc and water, and the inorganic phase was extracted with EtOAc. The combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub> yielding 210 mg (61%) 6-(3-Bromo-propoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 424 (MH<sup>+</sup>, 1Br, 1Cl).

#### 1.5

In analogy to example 1.4, 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester and 1,4-dibromobutane were converted to yield 6-(4-Bromo-butoxy)-

3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 438 (MH<sup>+</sup>, 1Br, 1Cl);

#### 1.6

In analogy to example 1.4, 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester and 1,5-dibromopentane (80%) were converted to yield 6-(5-Bromo-pentyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 451 (M, 1Br, 1Cl).

#### 1.7

To 153 mg (0.35 mmol) 6-(4-Bromo-but-2-enyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester in 3 ml DMF 71 mg (1 mmol) N-allylmethylamine and 140 mg (1 mmol) K<sub>2</sub>CO<sub>3</sub> (powdered) were added and the mixture was stirred at 60°C for 1h. The mixture was concentrated in vacuo, 8 ml acetone were added, the suspension was filtered and the filtrate was concentrated. Column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 yielded 95 mg (64%) 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 426 (M, 1Cl).

#### 1.8

To 210 mg (0.49 mmol) 6-(3-Bromo-propoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester in 5 ml DMF 191 µl (2 mmol) N-allylmethylamine and 106 mg (4.2 mmol, 50% in hexane) NaH were added. The mixture was stirred at RT for 4h and extracted with ether and water. The organic phase was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 yielded 70 mg (34%) 6-[3-(Allyl-methyl-amino)-propoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 415 (MH<sup>+</sup>, 1Cl).

#### 1.9

In analogy to example 1.8, 6-(5-Bromo-pentyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester and N-allylmethylamine were converted to yield 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 443 (MH<sup>+</sup>, 1Cl).

#### 1.10

240 mg (0.55 mmol) 6-(4-Bromo-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester and 260 µl (2.7 mmol) N-allylmethylamine were stirred in 5 ml DMF at RT for 3h. The mixture was extracted with ether and water, the organic phase was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 yielded 154 mg (66%) 6-[4-(Allyl-methyl-amino)-

butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 429 ( $MH^+$ , 1Cl).

## Example 2

### 2.1

- 5 To 9.7 g (65 mmol) 1,2,3,4-Tetrahydro-quinolin-6-ol in 90 ml  $CH_2Cl_2$  13.7 g (62.8 mmol) di-tert.-butyl-dicarbonate were added. The solution was stirred at 50°C for 5h and at RT over night. The mixture was concentrated and dissolved in  $Et_2O$ . A diluted aqueous solution of  $KHSO_4$  was added and the inorganic phase was extracted with  $Et_2O$ , the combined organic phases were washed with brine and dried over  $Na_2SO_4$ . Column chromatography on silica gel with  $CH_2Cl_2/MeOH$  9:1 yielded 16.2 g (99%) 6-Hydroxy-3,4-
- 10 dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as light yellow crystals, MS: 249 (M).

### 2.2

- To 11.6 g (46.5 mmol) 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl
- 15 ester in 200 ml acetone 18.6 g (134.8 mmol)  $K_2CO_3$  (powdered) and 13.7 g (115.7 mmol) 1,4-dibromobutane were added. The mixture was stirred at reflux for 4 h and at RT over night. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. EtOAc and water were added, the inorganic phase was extracted with EtOAc and the combined organic phases were washed with water and dried over  $Na_2SO_4$ . The crude product was
- 20 purified by column chromatography on silica gel with hexane/EtOAc 9:1 to yield 11.1 g (63%) 6-(4-Bromo-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as colorless oil, MS: 383 (M, 1Br).

### 2.3

- In analogy to example 2.2, 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-
- 25 butyl ester and 1,4-dibromobutene were converted to yield 6-(4-Bromo-but-2-enyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as colorless oil, MS: 381 (M, 1Br);

### 2.4

- In analogy to example 2.2, 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-
- 30 butyl ester and 1,5-dibromopentane were converted to yield 6-(5-Bromo-pentyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester (63%) as colorless oil, MS: 397 (M, 1Br);

### 2.5

- In analogy to example 2.2, 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-
- 35 butyl ester and 1,6-dibromohexane were converted to yield 6-(6-Bromo-hexyloxy)-3,4-

dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester (40%) as light green oil, MS: 412 ( $MH^+$ , 1Br);

## 2.6

1.5 g (3.75 mmol) 6-(5-Bromo-pentyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester were treated with 355 mg (5 mmol) N-allyl-methylamine and 830 mg (6 mmol)  $K_2CO_3$  (powdered) in 8 ml DMF at 60°C for 3h. The mixture was concentrated in vacuo, dissolved in acetone and filtered. The filtrate was concentrated and purified by column chromatography on silica gel with  $CH_2Cl_2/MeOH$  19:1 to yield 1.05 g (72%) 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as colorless oil, MS: 389 ( $MH^+$ ).

## 2.7

In analogy to example 2.6, 6-(6-Bromo-hexyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester and N-allyl-methylamine were converted to yield 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as colorless gum, MS: 403 ( $MH^+$ ).

## 2.8

In analogy to example 2.6, 6-(4-Bromo-but-2-enyloxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester and N-allyl-methylamine were converted to yield 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as colorless oil, MS: 373 ( $MH^+$ ).

## 2.9

5.0 g (13.0 mmol) 6-(4-Bromo-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester were treated with 3.66 g (51.5 mmol) N-allyl-methylamine in 100 ml DMF at 50°C for 30 min. The mixture was concentrated in vacuo, dissolved in  $Et_2O$  and water. The inorganic layer was extracted with  $Et_2O$ , and the combined organic phases were washed with water and dried over  $Na_2SO_4$ . Purification by column chromatography on silica gel with  $CH_2Cl_2/MeOH$  10:1 yielded 3.6 g (74%) 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as light yellow oil, MS: 375 ( $MH^+$ ).

## 2.10

In analogy to example 2.9, 6-(4-Bromo-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester and diethylamine were converted to yield 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as colorless oil.

**Example 3****3.1**

3.64 g (9.7 mmol) 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester in 5 ml CH<sub>2</sub>Cl<sub>2</sub> were treated with 3.5 ml TFA at 0°C, and  
5 the solution was stirred at 40°C for 1h. The solution was concentrated and the residue dissolved in a mixture of a saturated aqueous solution of NaHCO<sub>3</sub> and ether. The inorganic phase was extracted with ether and the combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub> to yield 1.85 g (69%) Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine, MS: 275 (MH<sup>+</sup>).

**10 3.2**

In analogy to example 3.1, 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester was converted to yield Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine (crude) as orange oil, MS: 273 (MH<sup>+</sup>).

**15 3.3**

In analogy to example 3.1, 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester was converted to yield Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-pentyl]-amine (82%) as light yellow oil, MS: 289 (MH<sup>+</sup>);

**20 3.4**

In analogy to example 3.1, 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester was converted to yield Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine (93%) as colorless gum, MS: 303 (MH<sup>+</sup>);

**25 3.5**

In analogy to example 3.1, 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester was converted to yield Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine as light brown oil, MS: 277 (MH<sup>+</sup>).

**3.6**

30 To 54 mg (0.2 mmol) Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine in 2 ml CH<sub>2</sub>Cl<sub>2</sub> 3 drops of Huenig's base and 527 mg (0.25 mmol) 4-chlorobenzene sulfonylchloride were added. The solution was stirred at RT for 2h, concentrated and purified by column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 19:1 to yield 70 mg (78%) Allyl-{4-[1-(4-chloro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-but-  
35 2-enyl}-methyl-amine as yellow oil, MS: 447 (MH<sup>+</sup>, 1Cl).

## 3.7

In analogy to example 3.6, Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine and 4-chlorobenzene sulfonylchloride were converted to yield Allyl-{5-[1-(4-chloro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pentyl}-methyl-amine  
5 (70%) as light yellow oil, MS: 462 (M, 1Cl).

## 3.8

To 60.4 mg (0.2 mmol) Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine in 2 ml  $\text{CH}_2\text{Cl}_2$  1 drop of Huenig's base and 57 mg (0.3 mmol) 4-chlorophenyl chloroformate in 1 ml  $\text{CH}_2\text{Cl}_2$  were added. The solution was stirred at RT for 30 min, was  
10 concentrated and the residue was dissolved in ether and a saturated aqueous solution of  $\text{NaHCO}_3$ . The inorganic phase was extracted with ether and the combined organic phases were washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Column chromatography on silica gel with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  19:1 yielded 46 mg (50%) 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 457  
15 ( $\text{MH}^+$ , 1Cl).

## 3.9

To 70 mg (0.25 mmol) Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine in 1.4 ml DMF 87  $\mu\text{l}$  (0.5 mmol) Huenig's base and 54  $\mu\text{l}$  (0.38 mmol) benzyl chloroformate were added. The solution was stirred at RT over night, was concentrated and the residue  
20 was dissolved in ether and 0.1M NaOH. The inorganic phase was extracted with ether and the combined organic phases were washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Column chromatography on silica gel with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  5:1 yielded 40 mg (38%) 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester as light yellow oil, MS: 411 ( $\text{MH}^+$ ).

## 25 3.10

In analogy to example 3.9, Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine and 4-chlorophenyl chloroformate were converted to yield 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-chloro-phenyl ester as colorless oil, MS: 431 ( $\text{MH}^+$ , 1Cl).

## 30 3.11

In analogy to example 3.9, Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine and hexylchloroformate were converted to yield 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid hexyl ester as colorless oil, MS: 405 ( $\text{MH}^+$ ).

## 3.12

35 In analogy to example 3.9, Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine



and 4-bromophenyl chloroformate were converted to yield 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-bromo-phenyl ester as colorless oil, MS: 475 ( $MH^+$ , 1Br).

### 3.13

- 5 In analogy to example 3.9, Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine and 4-fluorophenylchloroformate were converted to yield 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-fluoro-phenyl ester as colorless oil, MS: 415 ( $MH^+$ ).

### 3.14

- 10 In analogy to example 3.9, Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine and ethylchloroformate were converted to yield 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as brown oil, MS: 345 ( $MH^+$ ).

## Example 4

### 15 4.1

- To 1.0 g (4 mmol) 6-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester in 2.5 ml pyridine 0.72 ml (43.6 mmol) trifluoromethanesulfonic anhydride was added at 0°C and the mixture was stirred at RT over night. Water and Et<sub>2</sub>O were added, and the inorganic phase was extracted with Et<sub>2</sub>O. The combined organic phases were washed with  
20 2M HCl and water, and dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography on silica gel with hexane yielded 850 mg (56%) 6-Trifluoromethanesulfonyloxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as yellow solid, MS: 381 (M).

### 4.2

- To 850 mg (2.2 mmol) 6-Trifluoromethanesulfonyloxy-3,4-dihydro-2H-quinoline-1-  
25 carboxylic acid tert-butyl ester in 5 ml piperidine, 128.0 mg (0.1 mmol) tetrakis(triphenylphosphine)palladium followed by 21.0 mg (0.1 mmol) copper iodide were added. The solution was evaporated and flushed with argon prior to the addition of 210 µl (2.2 mmol) 4-pentynol at 80°C over a period of 45 min. Further 0.2 ml (2.1 mmol) 4-pentynol were added and the solution was stirred for 2h. The mixture was added to ice  
30 water, acidified with 2M HCl and extracted with ether. The combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by column chromatography with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 30:1 yielded 650 mg (92%) 6-(5-Hydroxy-pent-1-ynyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as light brown oil, MS: 316 ( $MH^+$ ).

### 4.3

- 35 850 mg (2.7 mmol) 6-(5-Hydroxy-pent-1-ynyl)-3,4-dihydro-2H-quinoline-1-carboxylic

acid tert-butyl ester in 30 ml ethanol were hydrogenated in the presence of 10% Pd/C over night. Purification by column chromatography yielded 450 mg (68%) 6-(5-Hydroxy-pentyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as yellow oil, MS: 319 (M).

## 5 4.4

To 450 mg (1.43 mmol) 6-(5-Hydroxy-pentyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester in 15 ml CH<sub>2</sub>Cl<sub>2</sub> 0.15 ml (1.9 mmol) methanesulfonyl chloride and 0.63 ml (4.5 mmol) triethylamine were added at 0°C. The solution was stirred at RT for 2h, was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and 1M HCl was added. The inorganic layer was extracted with  
10 CH<sub>2</sub>Cl<sub>2</sub> and the combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by column chromatography with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 30:1 yielded 560 mg (98%) 6-(5-Methanesulfonyloxy-pentyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as yellow oil, MS: 397 (M).

## 4.5

15 To 560 mg (1.4 mmol) 6-(5-Methanesulfonyloxy-pentyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester in 5 ml DMF were added 2.5 ml (26.0 mmol) N-allylmethylamine. The solution was stirred at 70°C for 2h, concentrated and dissolved in water and CH<sub>2</sub>Cl<sub>2</sub>. 2M NaOH was added and the inorganic phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by  
20 column chromatography with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1 yielded 470 mg (89%) 6-[5-(Allyl-methyl-amino)-pentyl]-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester as yellow oil, MS: 373 (MH<sup>+</sup>).

## 4.6

Treatment of 6-[5-(Allyl-methyl-amino)-pentyl]-3,4-dihydro-2H-quinoline-1-carboxylic  
25 acid tert-butyl ester with TFA in analogy to example 3.1 yielded Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yl)-pentyl]-amine as yellow oil, MS: 272 (M).

## 4.7

Reaction of Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yl)-pentyl]-amine with 4-Chlorobenzene-sulfonylchloride in analogy to example 3.6 yielded Allyl-[5-[1-(4-chloro-  
30 benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-pentyl]-methyl-amine as light yellow oil, MS: 447 (MH<sup>+</sup>, 1Cl);

## 4.8

Treatment of Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yl)-pentyl]-amine with 4-Bromobenzolsulfonylchloride in analogy to example 3.6 yielded Allyl-[5-[1-(4-bromo-

benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-pentyl}-methyl-amine as light brown oil, MS: 491 ( $MH^+$ , 1Br).

### Example 5

#### 5.1

5 In analogy to the method described by Gordon W. Gribble, Joseph H. Hoffmann Synthesis 1977, 859-860, the following reaction was performed. To a precooled solution of 22.3 g (0.1 mol) 5-benzyloxyindole in 270 ml acetic acid, 19 g (0.3 mol)  $NaCNBH_3$  were added. The solution was stirred at RT for 2h, the volume was reduced to one third and poured into 300 ml water. KOH was added under cooling and the solution was extracted with  
10 ether. The combined organic phases were washed with water, dried over  $Na_2SO_4$  and evaporated to yield 20.1 g (89%) 5-Benzyloxy-2,3-dihydro-1H-indole as colorless oil, MS: 225 (M).

#### 5.2

20 g (89 mmol) 5-Benzyloxy-2,3-dihydro-1H-indole in 250 ml  $CH_2Cl_2$  were treated with  
15 20 g (91.6 mmol) di-tert.-butyldicarbonate at 0°C for 1h and at RT for 1h. The mixture was concentrated and extracted with ether and 0.5 M HCl. The organic phase was washed with water and dried over  $Na_2SO_4$ . Trituration of the crude material with hexane yielded 23 g (71%) 5-Benzyloxy-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless solid, MS: 325 (M).

#### 5.3

20 23 g (68.6 mmol) 5-Benzyloxy-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 250 ml methanol were hydrogenated with 2.5 g 10% Pd/C for 2h. The suspension was filtered and the filtrate was concentrated and purified by column chromatography on silica gel with MeOH/EtOAc 1:1 yielding 14.4 g (90 %) 5-Hydroxy-2,3-dihydro-indole-1-  
25 carboxylic acid tert-butyl ester as colorless solid, MS: 235 (M).

#### 5.4

514 mg (2.3 mmol) 5-Hydroxy-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 12 ml DMF were treated with 830 mg (6 mmol) powdered  $K_2CO_3$  and 1070 mg (5 mmol) 1,4-dibromobutene. The suspension was stirred at 50°C for 3h, cooled to RT, diluted with  
30 ether and water. The aqueous phase was extracted with ether, the organic phases were washed with water and dried over  $Na_2SO_4$ . Column chromatography on silica gel with hexane/EtOAc 9:1 yielded 270 mg (31%) 5-(4-Bromo-but-2-enyloxy)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless solid, MS: 368 ( $MH^+$ , 1Br).

#### 5.5

35 214 mg (0.6 mmol) 5-(4-Bromo-but-2-enyloxy)-2,3-dihydro-indole-1-carboxylic acid

tert-butyl ester in 3 ml DMF were treated with 213 mg (3 mmol) N-allylmethylamine at 50°C for 0.5 h. The mixture was extracted with ether and water. The organic phase was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to yield 180 mg (83 %) 5-[4-(Allyl-methyl-amino)-but-2-enyloxy]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as yellow oil, MS: 359 (MH<sup>+</sup>).

## Example 6

### 6.1

Hydrogenation of 2.23 g (10 mmol) 5-benzyloxyindole in 25 ml acetic acid and 25 ml methanol with 500 mg 10% Pd/C yielded 2 g crude 2,3-Dihydro-1H-indol-5-ol.

### 6.2

To 0.7 g (5 mmol) 2,3-Dihydro-1H-indol-5-ol in 10 ml THF, 1.7 ml (10 mmol) N,N-diisopropylethylamine and 0.5 ml (3.6 mmol) 4-chlorophenyl-chloroformate were added at 0°C. The solution was stirred at RT for 1h and concentrated in vacuo. The residue was redissolved in ether/1M HCl, the inorganic phase was extracted with ether and the combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation yielded 420 mg (29 %) 5-Hydroxy-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as colorless solid, MS: 289 (M, 1Cl).

### 6.3

290 mg (1 mmol) 5-Hydroxy-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester in 5 ml acetone were treated with 320 mg (3 mmol) K<sub>2</sub>CO<sub>3</sub> (powdered) and 0.23 ml (2 mmol) 1,4-dibromobutane. The suspension was stirred at 50°C for 4h, cooled to RT, and was diluted with ether and water. The aqueous phase was extracted with ether, the organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography on silica gel with hexane/EtOAc 9:1 yielded 210 mg (49 %) 5-(4-Bromo-butoxy)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as colorless solid, MS: 423 (M, 1Br, 1Cl).

### 6.4

106 mg (0.25 mmol) 5-(4-Bromo-butoxy)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester in 2 ml DMF were treated with 71 mg (1 mmol) N-allylmethylamine at 50°C for 2 h. The mixture was concentrated and purified by column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 19:1 to give 68 mg (66 %) 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as colorless solid, MS: 415 (MH<sup>+</sup>, 1Cl).

## Example 7

## 7.1

9.41 g (40 mmol) 5-Hydroxy-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 90 ml acetone were treated with 16.6 g (6 mmol)  $K_2CO_3$  (powdered) and 17.3 g (5 mmol) 1,4-dibromobutane. The suspension was stirred at 50°C for 4h, cooled to RT, filtered and concentrated. Column chromatography on silica gel with  $CH_2Cl_2$  yielded 8.8 g (60%) 5-(4-Bromo-butoxy)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless solid, MS: 370 ( $MH^+$ , 1Br).

## 7.2

8.8 g (24 mmol) 5-(4-Bromo-butoxy)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 10 ml DMF were treated with 7.11 g (100 mmol) N-allylmethylamine at 50°C for 4 h. The solution was concentrated in vacuo and the residue was redissolved in ether and water. 2M NaOH was added and the inorganic phase was extracted with ether. The combined organic phases were washed with water, dried over  $Na_2SO_4$  and evaporated. Column chromatography with a gradient of  $CH_2Cl_2$ / MeOH 19:1 to 9:1 yielded 7.4 g (85 %) 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless oil, MS: 361 ( $MH^+$ ).

## 7.3

In analogy to example 7.2, 5-(4-Bromo-butoxy)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester and methoxyethyl-ethylamine were converted to yield 5-{4-[(2-Methoxyethyl)-methyl-amino]-butoxy}-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless oil, MS: 379 ( $MH^+$ ).

## 7.4

In analogy to example 7.2, 5-(4-Bromo-butoxy)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester and ethylaminoethanol were converted to yield 5-{4-[Ethyl-(2-hydroxyethyl)-amino]-butoxy}-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as yellow oil, MS: 379 ( $MH^+$ ).

## 7.5

To 7.3 g (20.2 mmol) 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 15 ml  $CH_2Cl_2$  10 ml trifluoroacetic acid were added at 0°C. The mixture was stirred at reflux for 3h and was concentrated in vacuo. Water and 2M NaOH were added and the inorganic phase was extracted with ether. The combined organic phases were washed with water and dried over  $Na_2SO_4$ . Evaporation yielded 5.2 g (98 %) Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine as orange oil, MS: 261 ( $MH^+$ ).

## 7.6

In analogy to example 7.5, 5-{4-[(2-Methoxy-ethyl)-methyl-amino]-butoxy}-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester was converted to yield [4-(2,3-Dihydro-1H-indol-5-yloxy)-butyl]-(2-methoxy-ethyl)-methyl-amine as light brown oil, MS: 279 (MH<sup>+</sup>).

## 5 7.7

In analogy to example 7.5, 5-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester was converted to yield 2-{[4-(2,3-Dihydro-1H-indol-5-yloxy)-butyl]-ethyl-amino}-ethanol as light yellow oil, MS: 279 (MH<sup>+</sup>).

## 7.8

- 10 220 mg (0.8 mmol) [4-(2,3-Dihydro-1H-indol-5-yloxy)-butyl]-(2-methoxy-ethyl)-methyl-amine in 0.5 ml dioxane were treated with 186 mg (0.9 mmol) chloro-thioformic acid (4-chloro-phenyl) ester in 0.5 ml dioxane at 0°C. The solution was stirred at RT for 3h, was diluted with water and ether and a saturated aqueous solution of NaHCO<sub>3</sub> was added. The inorganic layer was extracted with ether, washed with water and dried over
- 15 Na<sub>2</sub>SO<sub>4</sub>. Column chromatography with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 19:1 yielded 230 mg (64 %) 5-{4-[(2-Methoxy-ethyl)-methyl-amino]-butoxy}-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester as yellow viscous oil, MS: 449 (MH<sup>+</sup>, 1Cl).

## 7.9

- In analogy to example 7.8, 2-{[4-(2,3-Dihydro-1H-indol-5-yloxy)-butyl]-ethyl-amino}-ethanol and chloro-thioformic acid (4-chloro-phenyl) ester were converted to yield 5-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester as yellow viscous oil, MS: 449 (MH<sup>+</sup>, 1Cl).
- 20

## 7.10

- In analogy to example 7.8, Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine and chloro-thioformic acid (4-chloro-phenyl) ester were converted to yield 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester as light grey waxy solid, MS: 431 (MH<sup>+</sup>, 1Cl).
- 25

## 7.11

- In analogy to example 7.8, Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine and chloro-thioformic acid (4-chloro-phenyl) ester were converted to yield 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid O-(4-fluoro-phenyl) ester as light yellow viscous oil, MS: 415 (MH<sup>+</sup>).
- 30

## Example 8

## 8.1

4 g (20 mmol) 5-bromo-indoline in 50 ml  $\text{CH}_2\text{Cl}_2$  were treated with 4.4 g (20 mmol) di-tert.-butyldicarbonate at RT over night. The reaction mixture was concentrated in vacuo and triturated with hexane to yield 5.3 g (89%) 5-Bromo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless solid, MS: 297 (M, 1Br).

## 8.2

To 3.73 g (12.5 mmol) 5-Bromo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 25 ml piperidine 722 mg (0.63 mmol) tetrakis-(triphenylphosphine)-palladium and 120 mg (0.625 mmol) CuI were added. The solution was purged with argon and was heated to 80°C over a period of 45 min, during which 0.9 ml (9.4 mmol) 4-pentynol were added. Additional 0.9 ml (9.4 mmol) 4-pentynol were added and the mixture was stirred for 2h, poured into ice water and 2M HCl was added. The inorganic phase was extracted with ether, the combined organic phases were washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Purification on silica gel with hexane/EtOAc 4:1 to 2:1 yielded 3.0 g (79%) 5-(5-Hydroxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as light brown solid, MS: 302 ( $\text{MH}^+$ ). (See also: Stara, Irena G.; Sary, Ivo; Kollarovic, Adrian; Teply, Filip; Saman, David; Fiedler, Pavel. Coupling reactions of halobenzenes with alkynes. The synthesis of phenylacetylenes and symmetrical or unsymmetrical 1,2-diphenylacetylenes. Collect. Czech. Chem. Commun. (1999), 64(4), 649-672)

## 8.3

2.8 g (9.3 mmol) 5-(5-Hydroxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 60 ml MeOH were subjected to hydrogenation with 10%Pd/C to yield 2.8 g (quantitative) 5-(5-Hydroxy-pentyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless viscous oil, MS: 305 (M).

## 8.4

To 2.75 g (9 mmol) 5-(5-Hydroxy-pentyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 100 ml  $\text{CH}_2\text{Cl}_2$ , 0.87 ml (11 mmol) methanesulfonyl chloride and 3.8 ml (27 mmol) triethylamine were added at 0°C. The solution was concentrated in vacuo to yield crude 5-(5-Methanesulfonyloxy-pentyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as yellow viscous oil, MS: 384 ( $\text{MH}^+$ ). The crude material was dissolved in 5 ml DMF and 5 ml (50 mmol) N-allylmethylamine. The mixture was heated to 80°C for 3h, concentrated and the residue was dissolved in water and ether, 2M NaOH was added and the inorganic phase was extracted with ether. The combined organic phases were washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Column chromatography on silica gel with  $\text{CH}_2\text{Cl}_2$ :

MeOH 9:1 yielded 2.5 g (72%) 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester as colorless liquid, MS: 359 (MH<sup>+</sup>).

## 8.5

2.45 g (6.8 mmol) 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester in 5 ml CH<sub>2</sub>Cl<sub>2</sub> were treated with 4 ml TFA at 0°C. The solution was stirred at RT for 0.5h, and at 40 °C for 1h. The solution was concentrated and the residue was dissolved in ether and water. 2M NaOH was added and the inorganic phase was extracted with ether. The combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub> to yield 1.65 g (94%) Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine as light yellow oil, MS: 259 (MH<sup>+</sup>).

## 8.6

To 130 mg (0.5 mmol) Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine in 2 ml CH<sub>2</sub>Cl<sub>2</sub> 0.34 ml (2mmol) Huenig's base were added, followed by 0.28 ml (2 mmol) 4-chlorophenyl chloroformate. The solution was stirred at RT for 30 min, was concentrated and dissolved in 0.1 M NaOH and ether. The inorganic phase was extracted with ether. The combined organic phases were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 yielded 160 mg (77%) 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as light yellow oil, MS: 413 (MH<sup>+</sup>, 1Cl).

## 8.7

130 mg (0.5 mmol) Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine in 0.5 ml dioxane were treated with 0.072 ml (0.5 mmol) chlorothio-formic acid-O-(4-chlorophenyl)-ester at 15°C. The mixture was stirred for 15 min, concentrated and purified by column chromatography on silica gel with a gradient of CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99:1 to 97:3 to yield 92 mg 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester as colorless oil. The corresponding acetic acid salt was prepared by treatment with acetic acid in CH<sub>2</sub>Cl<sub>2</sub> to yield 101 mg 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester-acetic acid as light brown viscous oil, MS: 429 (MH<sup>+</sup>, 1Cl).



## Example 9

A solution of 0.153 mmol of the corresponding amine in 0.35 ml dry dioxane was treated with 0.23 mmol of the corresponding isocyanate in 0.54 ml dry dioxane. The solution was allowed to stand at room temperature over night. The resulting reaction mixture was  
 5 treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the resulting compound was obtained as amino formate.

| No. | Compound  | MS<br>MH <sup>+</sup> | Amine   | Isocyanate                      |
|-----|---|-----------------------|---|---------------------------------|
| 9.1 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (2,4-difluoro-phenyl)-amide  | 416                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 2,4 Difluorophenyl-isocyanate   |
| 9.2 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-fluoro-phenyl)-amide      | 398                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Fluorophenyl-isocyanate       |
| 9.3 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid p-tolylamide                 | 394                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Methylphenyl-isocyanate       |
| 9.4 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-bromo-phenyl)-amide       | 458<br>(1 Br)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Bromophenyl-isocyanate        |
| 9.5 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide | 440                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 2,4-Dimethoxy-phenyl-isocyanate |

|      |   |               |   |                                |
|------|---|---------------|---|--------------------------------|
| 9.6  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-methoxy-phenyl)-amide     | 410           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Methoxyphenyl-isocyanate     |
| 9.7  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid naphthalen-2-ylamide         | 430           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 2-Naphthylphenyl-isocyanate    |
| 9.8  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carboxylic acid (4-acetyl-phenyl)-amide      | 422           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Acetylphenyl-isocyanate      |
| 9.9  | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (2,4-difluoro-phenyl)-amide  | 414           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 2,4-Difluorophenyl-isocyanate  |
| 9.10 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-fluoro-phenyl)-amide      | 396           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Fluorophenyl-isocyanate      |
| 9.11 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid p-tolylamide                 | 392           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Methylphenyl-isocyanate      |
| 9.12 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-bromo-phenyl)-amide       | 456<br>(1 Br) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Bromophenyl-isocyanate       |
| 9.13 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide | 438           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 2,4-Dimethoxyphenyl-isocyanate |

|      |  |       |  |                             |
|------|--|-------|--|-----------------------------|
| 9.14 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-methoxy-phenyl)-amide              | 408   | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine              | 4-Methoxyphenyl-isocyanate  |
| 9.15 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid naphthalen-2-ylamide                  | 428   | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine              | 2-Naphthylphenyl-isocyanate |
| 9.16 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-acetyl-phenyl)-amide               | 420   | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine              | 4-Acetylphenyl-isocyanate   |
| 9.17 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-acetyl-phenyl)-amide  | 434   | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Acetylphenyl-isocyanate   |
| 9.18 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-methoxy-phenyl)-amide | 422.3 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Methoxyphenyl-isocyanate  |
| 9.19 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolylamide             | 406.3 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | p-Tolyl-isocyanate          |
| 9.20 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid naphthalen-1-ylamide     | 442.3 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 1-Naphthyl-isocyanate       |

|      |   |                 |   |  |
|------|---|-----------------|---|--|
| 9.21 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (2,4-difluoro-phenyl)-amide               | 428.3           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 2,4-Difluorophenyl-isocyanate                |
| 9.22 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluoro-3-trifluoromethyl-phenyl)-amide | 478.2           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluoro-3-Trifluoromethyl-Phenyl-isocyanate |
| 9.23 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluoro-phenyl)-amide                   | 410.2           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluorophenyl-isocyanate                    |
| 9.24 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide              | 452.3           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 2,4-Dimethoxy-phenyl-isocyanate              |
| 9.25 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-methylsulfanyl-phenyl)-amide           | 438.3           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-(Methylthio)-phenyl-isocyanate             |
| 9.26 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-bromo-phenyl)-amide                    | 470.1<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Bromophenyl-isocyanate                     |

|      |  |               |  |                            |
|------|--|---------------|--|----------------------------|
| 9.27 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid benzylamide            | 406.3         | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | Benzyl-isocyanate          |
| 9.28 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-butyl-phenyl)-amide | 448.2         | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-N-Butylphenyl-isocyanate |
| 9.29 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid phenethyl-amide        | 420           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | Phenethyl-isocyanate       |
| 9.30 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolylamide                | 436           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine      | 4-Tolyl-isocyanate         |
| 9.31 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluoro-phenyl)-amide     | 440           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine      | 4-Fluorophenyl-isocyanate  |
| 9.32 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-bromo-phenyl)-amide      | 500<br>(1 Br) | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine      | 4-Bromophenyl-isocyanate   |
| 9.33 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-butyl-phenyl)-amide      | 478           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine      | 4-Butylphenyl-isocyanate   |

|      |   |               |  |                                 |
|------|---|---------------|--|---------------------------------|
| 9.34 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (2,4-difluoro-phenyl)-amide  | 430           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 2,4-Difluorophenyl-isocyanate   |
| 9.35 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluoro-phenyl)-amide      | 412           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluorophenyl-isocyanate       |
| 9.36 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolylamide                 | 408           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Methylphenyl-isocyanate       |
| 9.37 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-bromo-phenyl)-amide       | 472<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Bromophenyl-isocyanate        |
| 9.38 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (2,4-dimethoxy-phenyl)-amide | 454           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 2,4-Dimethoxy-phenyl-isocyanate |
| 9.39 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-methoxy-phenyl)-amide     | 424           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Methoxyphenyl-isocyanate      |
| 9.40 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid naphthalen-2-ylamide         | 444           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 2-Naphthylphenyl-isocyanate     |
| 9.41 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-acetyl-phenyl)-amide      | 436           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Acetylphenyl-isocyanate       |

|      |   |               |   |                           |
|------|---|---------------|---|---------------------------|
| 9.42 | 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluorophenyl)-amide | 414           | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluorophenyl-isocyanate |
| 9.43 | 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolylamide           | 410           | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Methylphenyl-isocyanate |
| 9.44 | 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-bromophenyl)-amide  | 474<br>(1 Br) | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Bromophenyl-isocyanate  |

**Example 10**

- A solution of 0.153 mmol of the corresponding amine in 0.35 ml dry dioxane was treated with (0.46 mmol; 3 equivalents) Huenig's base and 0.2 mmol of the corresponding chloroformate in 0.54 ml dry dioxane. The solution was allowed to stand at room temperature over night and the resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the resulting compound was obtained as a mixture of amino hydrochloride and formate.

| No.  | Compound   | MS<br>MH+     | 1. Educt  | 2. Educt                    |
|------|--|---------------|---|-----------------------------|
| 10.1 | 6-[4-(allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-nitro-phenyl ester | 438           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Nitrophenyl-chloroformate |
| 10.2 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid hexyl ester          | 401           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | Hexyl-chloroformate         |
| 10.3 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-bromo-phenyl ester | 471<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Bromophenyl-chloroformate |
| 10.4 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid isobutyl ester       | 373           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | Isobutyl-chloroformate      |
| 10.5 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid phenyl ester         | 393           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | Phenyl-chloroformate        |



|       |  |               |   |   |
|-------|--|---------------|---|---|
| 10.6  | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxy-phenyl ester         | 423           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Methoxyphenyl-chloroformate           |
| 10.7  | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolyl ester                  | 407           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | P-Tolyl-chloroformate                   |
| 10.8  | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxycarbonyl-phenyl ester | 451           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Methoxy-carbonyl-phenyl chloroformate |
| 10.9  | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid butyl ester                    | 373           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | Butyl-chloroformate                     |
| 10.10 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-fluoro-phenyl ester          | 411           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluorophenyl-chloroformate            |
| 10.11 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-bromo-phenyl ester                | 501<br>(1 Br) | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine      | 4-Bromophenyl-chloroformate             |
| 10.12 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-fluoro-phenyl ester               | 441           | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine      | 4-Fluorophenyl-chloroformate            |

|       |   |     |  |                               |
|-------|---|-----|--|-------------------------------|
| 10.13 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid p-tolyl ester          | 437 | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | 4-Toloyl-chloroformate        |
| 10.14 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid hexyl ester            | 431 | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | Hexyl-chloroformate           |
| 10.15 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-methoxy-phenyl ester | 453 | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | 4-Methoxyphenyl-chloroformate |

## Example 11

A solution of 0.133 mmol of the corresponding amine in 0.5 ml dry DMF was treated subsequently with 0.17 mmol (1.3 equivalents) of the corresponding acid, 0.266 mmol (2 equivalents) Huenig's base, 0.266 mmol (2 equivalents) N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI) as well as catalytic amount of Hydroxybenzotriazole (HOBt) (approximately 0.02 mmol). The solution was allowed to stand at room temperature over night. The resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation, the resulting compound was obtained as a mixture of amino hydrochloride and formate.

| No.  | Compound   | MS<br>MH <sup>+</sup> | Amine   | Acid                               |
|------|--|-----------------------|---|------------------------------------|
| 11.1 | {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-bromo-phenyl)-methanone        | 443<br>(1 Br)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Bromobenzoic acid                |
| 11.2 | 3-{5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbonyl}-benzonitrile             | 390                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 3-Cyanobenzoic acid                |
| 11.3 | {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-methanone       | 383                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Fluorobenzoic acid               |
| 11.4 | {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(5-bromo-thiophen-2-yl)-methanone | 449<br>(1 Br)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 5-Bromothiophene-2-carboxylic acid |
| 11.5 | {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-chloro-phenyl)-methanone       | 399<br>(1 Cl)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Chloro-benzoic acid              |

|       |   |               |   |                                    |
|-------|---|---------------|---|------------------------------------|
| 11.6  | {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-phenyl-methanone                     | 365           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Benzoic acid                       |
| 11.7  | {5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indol-1-yl}-(4-trifluoromethyl-phenyl)-methanone | 433           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Trifluoromethyl benzoic acid     |
| 11.8  | {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(4-bromo-phenyl)-methanone           | 441<br>(1 Br) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Bromobenzoic acid                |
| 11.9  | 3-{5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbonyl}-benzonitrile                | 388           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 3-Cyanobenzoic acid                |
| 11.10 | {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-methanone          | 381           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Fluorobenzoic acid               |
| 11.11 | {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(5-bromo-thiophen-2-yl)-methanone    | 447<br>(1 Br) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 5-Bromothiophene-2-carboxylic acid |
| 11.12 | {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-(4-chloro-phenyl)-methanone          | 397<br>(1 Cl) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Chlorobenzoic acid               |
| 11.13 | {5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indol-1-yl}-phenyl-methanone                     | 363           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | Benzoic acid                       |

|       |  |               |   |                                    |
|-------|--|---------------|---|------------------------------------|
| 11.14 | 3-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carbonyl} -benzonitrile             | 402           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 3-Cyanobenzoic acid                |
| 11.15 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-bromo-phenyl)-methanone         | 455<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Bromobenzoic acid                |
| 11.16 | 1-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-2-(2,4-difluoro-phenyl)-ethanone | 427           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 2,4-Difluorophenyl acetic acid     |
| 11.17 | 1-(4-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-ethanone       | 419           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | Acetophenone-4-Carboxylic acid     |
| 11.18 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(5-bromo-thiophen-2-yl)-methanone  | 461<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 5-Bromothiophene-2-Carboxylic acid |
| 11.19 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(3-chloro-phenyl)-methanone        | 411<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 3-Chlorobenzoic acid               |

|       |  |               |   |                                  |
|-------|--|---------------|---|----------------------------------|
| 11.20 | 1-{6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-2-(4-fluoro-phenyl)-ethanone       | 409           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluorophenyl acetic acid       |
| 11.21 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-methanone          | 395           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluorobenzoic acid             |
| 11.22 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-chloro-phenyl)-methanone          | 411<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Chlorobenzoic acid             |
| 11.23 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-trifluoromethyl-phenyl)-methanone | 445           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-(Trifluoromethyl) Benzoic acid |
| 11.24 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-pyridin-3-yl-methanone               | 378           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | Nicotinic acid                   |
| 11.25 | {6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-3-methyl-phenyl)-methanone | 409           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluoro-3-Methyl benzoic acid   |

|       |   |               |  |                                    |
|-------|---|---------------|--|------------------------------------|
| 11.26 | 3-{6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carbonyl}-benzonitrile            | 432           | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | 3-Cyanophenyl benzoic acid         |
| 11.27 | {6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-bromophenyl)-methanone        | 485<br>(1 Br) | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | 4-Bromophenyl benzoic acid         |
| 11.28 | {6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(5-bromothiophen-2-yl)-methanone | 491<br>(1 Br) | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | 2-Bromothiophene-5-carboxylic acid |
| 11.29 | {6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluorophenyl)-methanone       | 425           | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | 4-Fluorophenyl benzoic acid        |
| 11.30 | {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-bromophenyl)-methanone          | 457<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Bromobenzoic acid                |
| 11.31 | 3-{6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbonyl}-benzonitrile              | 404           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 3-Cyanobenzoic acid                |
| 11.32 | {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluorophenyl)-methanone         | 397           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluorobenzoic acid               |

|       |   |               |   |                                    |
|-------|---|---------------|---|------------------------------------|
| 11.33 | {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(5-bromothiophen-2-yl)-methanone     | 463<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine | 5-Bromothiophene-2-carboxylic acid |
| 11.34 | {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-chlorophenyl)-methanone           | 413<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine | 4-Chlorobenzoic acid               |
| 11.35 | {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-phenyl-methanone                     | 379           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine | Benzoic acid                       |
| 11.36 | {6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinolin-1-yl}-(4-trifluoromethyl-phenyl)-methanone | 447           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine | 4-Trifluoromethyl benzoic acid     |
| 11.37 | (4-Bromo-phenyl)-[6-(4-diethylamino-butoxy)-3,4-dihydro-2H-quinolin-1-yl]-methanone                   | 459<br>(1 Br) | Diethyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine      | 4-Bromobenzoic acid                |
| 11.38 | 3-[6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carbonyl]-benzonitrile                        | 406           | Diethyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine      | 3-Cyanobenzoic acid                |



|       |  |               |   |                                    |
|-------|--|---------------|---|------------------------------------|
| 11.39 | [6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinolin-1-yl]-(4-fluorophenyl)-methanone        | 399           | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluorobenzoic acid               |
| 11.40 | (5-Bromo-thiophen-2-yl)-[6-(4-diethylamino-butoxy)-3,4-dihydro-2H-quinolin-1-yl]-methanone | 465<br>(1 Br) | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 5-Bromothiophene-2-carboxylic acid |

## Example 12

A solution of 0.133 mmol of the corresponding amine was treated with 0.17 mmol (1.3 equivalents) of the corresponding isothiocyanate in 0.35 ml dry dioxane. The solution was allowed to stand at room temperature over night, was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the compound was obtained as amino formate.

| No.  | Compound   | MS<br>MH <sup>+</sup> | Amine   | Isothiocyanate                          |
|------|--|-----------------------|---|---|
| 12.1 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (4-chloro-phenyl)-amide          | 430<br>(1 Cl)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Chlorophenyl-isothiocyanate           |
| 12.2 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid cycloheptylamide                 | 416                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Cycloheptyl-isothiocyanate              |
| 12.3 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid cyclohexylmethyl-amide           | 416                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Cyclohexane-methyl-isothiocyanate       |
| 12.4 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid 4-chloro-benzylamide             | 444<br>(1 Cl)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Chlorobenzyl-isothiocyanate           |
| 12.5 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (4-trifluoromethyl-phenyl)-amide | 464                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Trifluoromethyl-phenyl-isothiocyanate |

|       |  |               |   |   |
|-------|--|---------------|---|---|
| 12.6  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid 4-fluoro-benzylamide             | 428           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Fluorobenzyl-isothiocyanate           |
| 12.7  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid benzylamide                      | 410           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Benzyl-isothiocyanate                   |
| 12.8  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid cyclohexylamide                  | 402           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Cyclohexyl-isothiocyanate               |
| 12.9  | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid (4-chloro-phenyl)-amide          | 428<br>(1 Cl) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Chlorophenyl-isothiocyanate           |
| 12.10 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid cycloheptylamide                 | 414           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | Cycloheptyl-isothiocyanate              |
| 12.11 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid cyclohexylmethyl-amide           | 414           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | Cyclohexanemethyl-isothiocyanate        |
| 12.12 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid 4-chloro-benzylamide             | 442<br>(1 Cl) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Chlorobenzyl-isothiocyanate           |
| 12.13 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid (4-trifluoromethyl-phenyl)-amide | 462           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Trifluoromethyl-phenyl-isothiocyanate |

|       |  |     |   |                                   |
|-------|--|-----|---|-----------------------------------|
| 12.14 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid 4-fluorobenzylamide      | 426 | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Fluorobenzyl-isothiocyanate     |
| 12.15 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (3-methyl-butyl)-amide   | 390 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 1-Isothiocyanato-3-methyl-butane  |
| 12.16 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (furan-2-ylmethyl)-amide | 400 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 2-Furfuryl-isothiocyanate         |
| 12.17 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid ethylamide               | 348 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Isithiocyanato-ethane             |
| 12.18 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid butylamide               | 376 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Isithiocyanato-butane             |
| 12.19 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (2-methyl-butyl)-amide   | 390 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 1-Isithiocyanato-2-methyl-butane  |
| 12.20 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (2-methoxy-ethyl)-amide  | 378 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 1-Isithiocyanato-2-methoxy-ethane |
| 12.21 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (4-butyl-phenyl)-amide   | 452 | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 1-Butyl-4-isithiocyanato-benzene  |

|       |  |               |  |  |
|-------|--|---------------|--|--|
| 12.22 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (tetrahydro-furan-2-ylmethyl)-amide    | 404           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine        | 2-Tetrahydro-furfuryl-isothiocyanate   |
| 12.23 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid (4-chloro-phenyl)-amide          | 444<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Chlorophenyl-isothiocyanat           |
| 12.24 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid cycloheptylamide                 | 430           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | Cycloheptyl-isothiocyanat              |
| 12.25 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid cyclohexylmethyl-amide           | 430           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | Cyclohexane-methyl-isothiocyanate      |
| 12.26 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid 4-chloro-benzylamide             | 458<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Chlorobenzyl-isothiocyanate          |
| 12.27 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid (4-trifluoromethyl-phenyl)-amide | 478           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Trifluoromethyl-phenyl-isothiocyanat |
| 12.28 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid 4-fluoro-benzylamide             | 442           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluorobenzyl-isothiocyanate          |

|       |   |               |  |                               |
|-------|---|---------------|--|-------------------------------|
| 12.29 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid benzylamide               | 424           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | Benzyl-isothiocyanate         |
| 12.30 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid cyclohexylamide           | 416           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | Cyclohexyl-isothiocyanate     |
| 12.31 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid (4-chloro-phenyl)-amide | 472<br>(1 Cl) | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | p-Chlorophenyl-isothiocyanate |
| 12.32 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid cycloheptylamide        | 458           | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine | Cycloheptyl-isothiocyanate    |

## Example 13

A solution of 0.14 mmol of the corresponding amine in 0.5 ml dry dioxane was treated with a solution of 0.14 mmol of the corresponding chlorothionoformate in 0.35 ml dry dioxane. The solution was allowed to stand at room temperature over night, treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the compound was obtained as a mixture of amino hydrochloride and formate.

| No.  | Compound  | MS<br>MH <sup>+</sup> | Amine   | Chloro-<br>thionoformate             |
|------|---|-----------------------|---|--------------------------------------|
| 13.1 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-fluoro-phenyl) ester | 413                   | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine     | 4-Fluorophenyl-chloro-thionoformate  |
| 13.2 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-phenyl ester            | 395                   | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine     | Phenyl-chloro-thionoformate          |
| 13.3 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-p-tolyl ester           | 409                   | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine     | p-Toloyl-chloro-thionoformate        |
| 13.4 | 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-fluoro-phenyl) ester   | 431                   | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluoro-phenyl-chloro-thionoformate |
| 13.5 | 6-(4-Diethylamino-butoxy)-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-chloro-phenyl) ester   | 447<br>(1 Cl)         | Diethyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Chloro-phenyl-chloro-thionoformate |

|      |   |               |  |                                      |
|------|---|---------------|--|--------------------------------------|
| 13.6 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-fluoro-phenyl) ester | 429           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluoro-phenyl-chloro-thionoformate |
| 13.7 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid O-(4-chloro-phenyl) ester | 445<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Chloro-phenyl-chloro-thionoformate |
| 13.8 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-carbothioic acid O-phenyl ester            | 411           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | Phenyl-chloro-thionoformate          |



## Example 14

- A solution of 0.135 mmol of the corresponding amine in 0.75 ml dry dioxane was treated with 5 equivalents of triethylamine followed by a solution of 0.175 mmol (1.3 equivalent) of the corresponding sulfamoylchloride in 0.25 ml dry dioxane. The suspension was
- 5 allowed to stand at room temperature over night, treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the resulting compound was obtained as a mixture of amino hydrochloride and formate.

| No.  | Compound   | MS<br>MH <sup>+</sup> | Amine   | Sulfamoylchloride                    |
|------|--|-----------------------|---|--------------------------------------|
| 14.1 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-chloro-phenyl)-amide     | 450<br>(1 Cl)         | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Chlorophenyl-sulfamoylchloride     |
| 14.2 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid p-tolylamide                | 430                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Methylphenyl-sulfamoylchloride     |
| 14.3 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-cyano-phenyl)-amide      | 441                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Cyanophenyl-sulfamoylchloride      |
| 14.4 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-methoxy-phenyl)-amide    | 446                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Methoxyphenyl-sulfamoylchloride    |
| 14.5 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (3,4-difluoro-phenyl)-amide | 452                   | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 3,4-Difluorophenyl-sulfamoylchloride |

|       |  |               |   |                                      |
|-------|--|---------------|---|--------------------------------------|
| 14.6  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (3-fluoro-phenyl)-amide     | 434           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 3-Fluorophenyl-sulfamoylchloride     |
| 14.7  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (2,4-difluoro-phenyl)-amide | 452           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 2,4-Difluorophenyl-sulfamoylchloride |
| 14.8  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (2,5-difluoro-phenyl)-amide | 452           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 2,5-Difluorophenyl-sulfamoylchloride |
| 14.9  | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid (4-bromo-phenyl)-amide      | 494<br>(1 Br) | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | 4-Bromophenyl-sulfamoylchloride      |
| 14.10 | 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-sulfonic acid phenylamide                 | 416           | Allyl-[4-(2,3-dihydro-1H-indol-5-yloxy)-butyl]-methyl-amine | Phenyl-sulfamoylchloride             |
| 14.11 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid phenylamide                 | 414           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | Phenyl-sulfamoylchloride             |
| 14.12 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid (4-chloro-phenyl)-amide     | 448<br>(1 Cl) | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 4-Chlorophenyl-sulfamoylchloride     |
| 14.13 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid (2,4-difluoro-phenyl)-amide | 450           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine   | 2,4-Difluorophenyl-sulfamoylchloride |

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|-------|--|---------------|--|--------------------------------------|
| 14.14 | 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-sulfonic acid (4-fluorophenyl)-amide                  | 432           | Allyl-[5-(2,3-dihydro-1H-indol-5-yl)-pentyl]-methyl-amine              | 4-Fluorophenyl-sulfamoylchloride     |
| 14.15 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chlorophenyl)-amide     | 462<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Chlorophenyl-sulfamoylchloride     |
| 14.16 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-fluorophenyl)-amide     | 446           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Fluorophenyl-sulfamoylchloride     |
| 14.17 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-bromophenyl)-amide      | 506<br>(1 Br) | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Bromophenyl-sulfamoylchloride      |
| 14.18 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (p-tolyl)-amide            | 442           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | p-tolyl-sulfamoylchloride            |
| 14.19 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3,4-difluorophenyl)-amide | 464           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 3,4-Difluorophenyl-sulfamoylchloride |

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|-------|--|-----|--|--|
| 14.20 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide | 496 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Trifluoromethyl-phenyl-sulfamoylchloride |
| 14.21 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3-fluorophenyl)-amide           | 446 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 3-Fluorophenyl-sulfamoylchloride           |
| 14.22 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-cyanophenyl)-amide            | 453 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Cyanophenyl-sulfamoylchloride            |
| 14.23 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluorophenyl)-amide       | 464 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 2,4-Difluorophenyl-sulfamoylchloride       |
| 14.24 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-methoxyphenyl)-amide          | 458 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 4-Methoxyphenyl-sulfamoylchloride          |
| 14.25 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,5-difluorophenyl)-amide       | 464 | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | 2,5-Difluorophenyl-sulfamoylchloride       |

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|-------|--|---------------|--|--|
| 14.26 | 6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (phenyl)-amide               | 428           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-but-2-enyl]-amine | Phenyl-sulfamoylchloride                   |
| 14.27 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-phenyl)-amide          | 478<br>(1 Cl) | Allyl-methyl-[5-(1,2,3,4-tetrahydroquinolin-6-yloxy)-pentyl]-amine     | 4-Chlorophenyl-sulfamoylchloride           |
| 14.28 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-bromo-phenyl)-amide           | 522<br>(1 Br) | Allyl-methyl-[5-(1,2,3,4-tetrahydroquinolin-6-yloxy)-pentyl]-amine     | 4-Bromophenyl-sulfamoylchloride            |
| 14.29 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid p-tolylamide acid                | 458           | Allyl-methyl-[5-(1,2,3,4-tetrahydroquinolin-6-yloxy)-pentyl]-amine     | 4-Methylphenyl-sulfamoylchloride           |
| 14.30 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-trifluoromethyl-phenyl)-amide | 512           | Allyl-methyl-[5-(1,2,3,4-tetrahydroquinolin-6-yloxy)-pentyl]-amine     | 4-Trifluoromethyl-phenyl-sulfamoylchloride |
| 14.31 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-cyano-phenyl)-amide           | 469           | Allyl-methyl-[5-(1,2,3,4-tetrahydroquinolin-6-yloxy)-pentyl]-amine     | 4-Cyanophenyl-sulfamoylchloride            |
| 14.32 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-methoxy-phenyl)-amide         | 474           | Allyl-methyl-[5-(1,2,3,4-tetrahydroquinolin-6-yloxy)-pentyl]-amine     | 4-Methoxyphenyl-sulfamoylchloride          |

|       |   |               |   |                                      |
|-------|---|---------------|---|--------------------------------------|
| 14.33 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-fluoro-phenyl)-amide     | 462           | Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-pentyl]-amine | 4-Fluorophenyl-sulfamoylchloride     |
| 14.34 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3,4-difluoro-phenyl)-amide | 480           | Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-pentyl]-amine | 3,4-Difluorophenyl-sulfamoylchloride |
| 14.35 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3-fluoro-phenyl)-amide     | 462           | Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-pentyl]-amine | 3-Fluorophenyl-sulfamoylchloride     |
| 14.36 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluoro-phenyl)-amide | 480           | Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-pentyl]-amine | 2,4-Difluorophenyl-sulfamoylchloride |
| 14.37 | 6-[5-(Allyl-methyl-amino)-pentyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,5-difluoro-phenyl)-amide | 480           | Allyl-methyl-[5-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-pentyl]-amine | 2,5-Difluorophenyl-sulfamoylchloride |
| 14.38 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-cyano-phenyl)-amide       | 483           | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine  | 4-Cyanophenyl-sulfamoylchloride      |
| 14.39 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-methoxy-phenyl)-amide     | 488           | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine  | 4-Methoxyphenyl-sulfamoylchloride    |
| 14.40 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-phenyl)-amide      | 492<br>(1 Cl) | Allyl-methyl-[6-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-hexyl]-amine  | 4-Chlorophenyl-sulfamoylchloride     |

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|-------|--|---------------|---|--------------------------------------|
| 14.41 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,5-difluoro-phenyl)-amide | 494           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | 2,5-Difluorophenyl-sulfamoylchloride |
| 14.42 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-bromo-phenyl)-amide      | 536<br>(1 Br) | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | 4-Bromophenyl-sulfamoylchloride      |
| 14.43 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluoro-phenyl)-amide | 494           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | 2,4-Difluorophenyl-sulfamoylchloride |
| 14.44 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid p-tolylamide                | 472           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | p-Tolyl-sulfamoylchloride            |
| 14.45 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid butylamide                  | 438           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | Butyl-sulfamoylchloride              |
| 14.46 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (3-fluoro-phenyl)-amide     | 476           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | 3-Fluorophenyl-sulfamoylchloride     |
| 14.47 | 6-[6-(Allyl-methyl-amino)-hexyloxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid phenylamide                 | 458           | Allyl-methyl-[6-(1,2,3,4-tetrahydroquinolin-6-yloxy)-hexyl]-amine | Phenyl-sulfamoylchloride             |
| 14.48 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid phenylamide                   | 430           | Allyl-methyl-[4-(1,2,3,4-tetrahydroquinolin-6-yloxy)-butyl]-amine | Phenyl-sulfamoylchloride             |

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|-------|--|---------------|--|--------------------------------------|
| 14.49 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-chloro-phenyl)-amide     | 464<br>(1 Cl) | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Chlorophenyl-sulfamoylchloride     |
| 14.50 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (2,4-difluoro-phenyl)-amide | 466           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 2,4-Difluorophenyl-sulfamoylchloride |
| 14.51 | 6-[4-(Allyl-methyl-amino)-butoxy]-3,4-dihydro-2H-quinoline-1-sulfonic acid (4-fluoro-phenyl)-amide     | 448           | Allyl-methyl-[4-(1,2,3,4-tetrahydro-quinolin-6-yloxy)-butyl]-amine | 4-Fluorophenyl-sulfonamylchoride     |



**Example 15**

Sulfamoyl chlorides were prepared according to the following procedure. 3 equivalents of the corresponding amine were dissolved in  $\text{CH}_2\text{Cl}_2$  (1 ml/mmol) and placed in an ice bath. A solution of chlorosulfonic acid (1 eq.) in  $\text{CH}_2\text{Cl}_2$  (0.5 ml / mmol) was added slowly (30 min). The reaction mixture was stirred at 0 °C for a further 30 min. Afterwards, the ice bath was removed and the stirring was continued for 1 h at room temperature. The precipitate was collected by filtration and dried under high vacuum. This salt was suspended in toluene (1 ml / mmol amine) and  $\text{PCl}_5$  (1 eq) was added. The mixture was stirred at 75 °C for 2 h, cooled to room temperature and filtered. The solid residue was washed with toluene. The filtrate was evaporated and dried under high vacuum. The resulting crude sulfamoyl chloride was used in the next step without further purification. The following sulfamoyl chlorides were prepared from the corresponding amines:

Phenylsulfamoyl chloride, 2,4-Difluoro-phenylsulfamoyl chloride, 2,5-Difluoro-phenylsulfamoyl chloride, 3,4-Difluoro-phenylsulfamoyl chloride, 3-Fluoro phenyl-sulfamoyl chloride, 4-Fluoro-phenylsulfamoyl chloride, 4-Chloro-phenylsulfamoyl chloride, 4-Bromo-phenylsulfamoyl chloride, 4-Methyl-phenylsulfamoyl chloride, 4-trifluoromethyl-phenylsulfamoyl chloride, 4-Cyano-phenylsulfamoyl chloride, 4-Methoxy-phenylsulfamoyl chloride, Butylsulfamoyl chloride.

**Example 16****16.1**

To 33.3 g (0.3 mol) 3-fluoroaniline in 160 ml  $\text{CH}_2\text{Cl}_2$  were added 450 ml of a 0.7 M aqueous  $\text{NaHCO}_3$ -solution. The resulting mixture was treated dropwise with 34.6 ml (0.41 mol) methylchloroformate within a period of 20 min. After stirring overnight the layers were separated and the organic layer was washed with saturated aqueous NaCl and dried with  $\text{MgSO}_4$ . After evaporation of ca. 60% of the solvent, 600 ml of hexane were added, whereby (3-Fluoro-phenyl)-carbamic acid methyl ester precipitated as a colorless solid that was filtered off and dried i.v. (41 g (81%)).

The solid was dissolved in 600 ml acetonitrile and treated subsequently with 50 g (0.28 mmol) N-bromosuccinimide and 2.13 ml (0.024 mol) trifluormethane sulfonic acid. After stirring at room temperature during 12 hours, ca. 50% of the solvent were evaporated, the resulting mixture diluted with 1000 ml EtOAc, and washed subsequently with saturated aqueous  $\text{NaHCO}_3$  and saturated aqueous NaCl. Drying of the combined organic layers with  $\text{MgSO}_4$ , evaporation of the solvent, and column chromatography of the residue on silica gel with hexane/EtOAc 8:1 and then 2:1 gave 39 g (64%) (4-Bromo-3-fluoro-phenyl)-carbamic acid methyl ester as a colorless solid. The solid was dissolved in 390 ml

acetonitrile, treated subsequently with 39 g (0.172 mol) N-iodosuccinimide and 1.4 ml (0.016 mol) trifluormethanesulfonic acid at 0°C and left to stir at room temperature during 10 hours. Cooling the reaction mixture to 0°C led to precipitation of (4-Bromo-5-fluoro-2-iodo-phenyl)-carbamic acid methyl ester as colorless crystals that were filtered off and dried (26.7g, 44%). Dilution of the filtrate with 600 ml hexane followed by subsequent washing with saturated aqueous NaHCO<sub>3</sub> and 0.5M aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, drying of the organic layer with MgSO<sub>4</sub>, evaporation of the solvent, and recrystallization of the residue in acetonitrile gave an additional 6.3 g (12%) of (4-Bromo-5-fluoro-2-iodo-phenyl)-carbamic acid methyl ester (total: 33g, 56%), MS: 373 (M, 1Br).

## 10 16.2

A mixture of 70 mg (0.1 mmol) Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and 27 mg (0.142 mmol) CuI in triethylamine was refluxed under argon during 20 min, cooled to 0°C, treated with 7g (0.019 mmol) (4-Bromo-5-fluoro-2-iodo-phenyl)-carbamic acid methyl ester, stirred 10 min at room temperature, treated with 2.95 (0.021 mmol) ethynyltrimethylsilane, and stirred 1 h at room temperature. 2M aqueous HCl and ice were added and the mixture extracted three times with EtOAc. The combined organic layers were washed subsequently with H<sub>2</sub>O and saturated aqueous NaCl, dried with MgSO<sub>4</sub> and the solvent was evaporated. The crude product obtained was dissolved in 50 ml tert-butanol, treated with 3.2 g (0.023 mol) KOH and the resulting mixture refluxed for 1.5 h. The solvent was evaporated and the residue distributed between icy water and Et<sub>2</sub>O. The organic layer was washed with water and dried with MgSO<sub>4</sub>. Evaporation of the solvent and column chromatography on silica gel with hexane/EtOAc 9:1 gave of 3.2 g (80%) 5-Bromo-6-fluoro-1H-indole, MS: 213 (M, 1Br).

## 16.3

25 To a solution of 2.1 g (9.81 mmol) 5-Bromo-6-fluoro-indole in 35 ml of DMF were added 1.54 g (13.76 mmol) KOtBu and 3.0 g (13.76 mmol) Di-tert.butylcarbonate, and the solution was stirred for 1 hr at room temperature and 30 min at 60°C. The mixture was poured into water, acidified with 2M aqueous HCl and extracted with Et<sub>2</sub>O. Drying of the organic layers with MgSO<sub>4</sub>, evaporation of the solvent, and chromatography on silica gel with hexane/EtOAc 49:1 gave 2.6 g (84%) 5-Bromo-6-fluoro-indole-1-carboxylic acid tert-butyl ester as a colorless liquid, MS: 313 (M, 1Br).

## 16.4

A mixture of 3.04 g (9.67 mmol) 5-Bromo-6-fluoro-indole-1-carboxylic acid tert-butyl ester, 670 mg (0.58 mmol) Pd(PPh<sub>3</sub>)<sub>4</sub>, and 111 mg (0.58 mmol) CuI in 25 ml of piperidine was heated to 60°C, treated with 1.61 ml (1.80 mmol) 4-pentyne-1-ol and stirred at 80°C for 2 hrs. After cooling to room temperature the mixture was poured into water, acidified with 2M aqueous HCl and extracted with EtOAc. Drying of the combined organic layers

with  $\text{MgSO}_4$ , evaporation of the solvent, and chromatography on silica gel with  $\text{CH}_2\text{Cl}_2$  gave 2.6 g (85%) of 6-Fluoro-5-(5-hydroxy-pent-1-ynyl)-indole-1-carboxylic acid tert-butyl ester as a viscous orange oil, MS: 318 ( $\text{MH}^+$ ).

## 16.5

- 5 A solution of 950 mg (0.3 mmol) 6-Fluoro-5-(5-hydroxy-pent-1-ynyl)-indole-1-carboxylic acid tert-butyl ester in 20 ml EtOH was treated with 2 ml of saturated aqueous NaOH and stirred during 2 hours at 60°C. 75% of the solvent were evaporated, the resulting mixture was poured into 5 ml of water, acidified with 2M aqueous HCl, and extracted with EtOAc. Drying of the combined organic layers with  $\text{MgSO}_4$ , evaporation of  
10 the solvent, and chromatography on silica gel with  $\text{CH}_2\text{Cl}_2$  gave 550 mg (84%) of 5-(6-Fluoro-1H-indol-5-yl)-pent-4-yn-1-ol as a viscous light yellow oil, MS: 218 (M).

## 16.6

- A solution of 109 mg (0.5 mmol) 5-(6-Fluoro-1H-indol-5-yl)-pent-4-yn-1-ol in 3 ml AcOH/TFA 2:1 was cooled to 0°C, treated with  $\text{NaCNBH}_3$  and stirred for 1 hour at room  
15 temperature. The mixture was poured into icy water, made strongly alkaline by the addition of 2M NaOH, and extracted with EtOAc. Drying of the combined organic layers with  $\text{MgSO}_4$ , evaporation of the solvent, and chromatography on silica gel with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  49:1 gave 80 mg (73%) of 5-(6-Fluoro-2,3-dihydro-1H-indol-5-yl)-pent-4-yn-1-ol as a colorless oil, MS: 220 ( $\text{MH}^+$ ).

## 20 16.7

- A solution of 99 mg (0.45 mmol) 5-(6-Fluoro-2,3-dihydro-1H-indol-5-yl)-pent-4-yn-1-ol and 0.155 ml (0.90 mmol) N-Ethyldiisopropylamine in 2 ml  $\text{CH}_2\text{Cl}_2$  was treated with 0.125 ml (0.90 mmol) 4-chlorophenyl chloroformate and stirred at room temperature during 1 hour. The mixture was poured into water, extracted with EtOAc and the combined organic  
25 layers were dried with  $\text{MgSO}_4$ . Evaporation of the solvent, chromatography on silica gel with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  49:1 gave 125 mg (74%) of 6-Fluoro-5-(5-hydroxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as a viscous light yellow oil, MS: 374 ( $\text{MH}^+$ , 1Cl).

## 16.8

- 30 In analogy to example 16.7, 5-(6-Fluoro-2,3-dihydro-1H-indol-5-yl)-pent-4-yn-1-ol and toluene-4-sulfonylchloride gave 5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-yn-1-ol, MS: 374 ( $\text{MH}^+$ , 1Cl).

## 16.9

- A solution of 120 mg (0.321 mmol) 6-Fluoro-5-(5-hydroxy-pent-1-ynyl)-2,3-dihydro-  
35 indole-1-carboxylic acid 4-chloro-phenyl ester and 0.164 ml (0.96 mmol) N-

ethyl-diisopropylamine in 2 ml  $\text{CH}_2\text{Cl}_2$  was treated with 0.03 ml (0.385 mmol) of methanesulfonyl chloride and stirred at room temperature for 1 hour. The mixture was poured into  $\text{Et}_2\text{O}$  and washed with 0.5 M HCl. Drying of the organic layer with  $\text{MgSO}_4$ , evaporation of the solvent, and chromatography on silica gel with  $\text{CH}_2\text{Cl}_2$  gave 91 mg (61%) of 6-Fluoro-5-(5-methanesulfonyloxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as a colorless oil, MS: 452 ( $\text{MH}^+$ , 1Cl).

## 16.10

A solution of 30 mg (0.066 mmol) of 6-Fluoro-5-(5-methanesulfonyloxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester and 0.1 ml (0.10 mmol) N-methylallylamine in 0.5 ml of DMF was stirred at 80°C for 2 hours. The mixture was poured into 0.5 M aqueous NaOH and extracted with EtOAc. Drying of the combined organic layers with  $\text{MgSO}_4$ , evaporation of the solvent, and chromatography on silica gel with EtOAc/MeOH/ $\text{NEt}_3$  10:1:0.1 gave 19 mg (67%) of 5-[5-(Allyl-methyl-amino)-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as a light brown oil, MS: 427 ( $\text{MH}^+$ , 1Cl).

## 16.11

In analogy to example 16.10, 6-Fluoro-5-(5-methanesulfonyloxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester and 2-(methylamino)ethanol were converted to yield 6-Fluoro-5-{5-[(2-hydroxy-ethyl)-methyl-amino]-pent-1-ynyl}-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as a colorless oil, MS: 430 (M, 1Cl).

## 16.12

In analogy to example 16.11, 6-Fluoro-5-(5-methanesulfonyloxy-pent-1-ynyl)-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester and 2(ethylamino)ethanol were converted to yield 5-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pent-1-ynyl}-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester as a colorless oil, MS: 445 ( $\text{MH}^+$ , 1 Cl).

## 16.13

A solution of 50 mg (0.141 mmol) of 5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-yn-1-ol and 0.072 ml (0.42 mmol) diisopropyl ethylamine in 2 ml  $\text{CH}_2\text{Cl}_2$  was treated at 0°C with 0.033 ml (0.42 mmol) methanesulfonylchloride and stirred at room temperature for one hour. Addition of aqueous 0.1M HCl, extraction with  $\text{Et}_2\text{O}$ , drying of the organic layer with  $\text{MgSO}_4$ , and evaporation of the solvent gave 60 mg of Methanesulfonic acid 5-[6-fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-ynyl ester as brown oil of which 12 mg were dissolved in 0.5 ml DMF, treated with 0.043 ml (0.053 mmol) 2-(methylamino)ethanol and stirred at 80°C during 2 hours.

Evaporation of the solvent and excess 2-(methylamino)ethanol and chromatography on silica gel with EtOAc/MeOH/NEt<sub>3</sub> 10:1:0.1 gave 10 mg (82%) of 2-({5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-ynyl}-methyl-amino)-ethanol as a light yellow oil, MS: 431 (MH<sup>+</sup>).

5 16.14

In analogy to example 16.13, 5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-yn-1-ol and 2-(ethylamino)ethanol instead of 2-(methylamino)ethanol were converted to yield 2-(Ethyl-{5-[6-fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-ynyl}-amino)-ethanol as a light yellow oil, MS: 445 (MH<sup>+</sup>).

10 Example 17

17.1

Hydrogenolysis at atmospheric pressure of 5 mg (0.013 mmol) 5-[5-(Allyl-methyl-amino)-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester in 0.5 ml AcOH in the presence of 5 mg 10% Pd/C during 12 hrs, followed by filtration,  
15 evaporation of the AcOH, distribution of the residue between Et<sub>2</sub>O and 0.5 M NaOH, drying of the organic layer with Na<sub>2</sub>SO<sub>4</sub>, evaporation of the solvent and chromatography on silica gel with EtOAc/MeOH/NEt<sub>3</sub> 10:1:0.1 gave 3 mg (64%) of 6-Fluoro-5-[5-(methyl-propyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid phenyl ester as a yellow oil, MS: 399 (MH<sup>+</sup>)

20 17.2

In analogy to example 17.1, hydrogenolysis of 2-({5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pent-4-ynyl}-methyl-amino)-ethanol yielded 2-({5-[6-Fluoro-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-indol-5-yl]-pentyl}-methyl-amino)-ethanol. MS: 435 (MH<sup>+</sup>).

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

| <u>Ingredients</u>    | <u>Per tablet</u> |
|-----------------------|-------------------|
| Compound of formula I | 10.0 - 100.0 mg   |
| Lactose               | 125.0 mg          |
| Maize starch          | 75.0 mg           |
| Talc                  | 4.0 mg            |
| Magnesium stearate    | 1.0 mg            |

5

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

| <u>Ingredients</u>    | <u>Per capsule</u> |
|-----------------------|--------------------|
| Compound of formula I | 25.0 mg            |
| Lactose               | 150.0 mg           |
| Maize starch          | 20.0 mg            |
| Talc                  | 5.0 mg             |

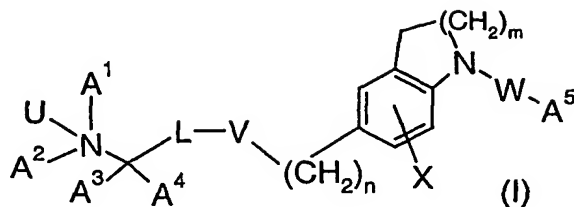
Example C

10 Injection solutions can have the following composition:

|                               |           |
|-------------------------------|-----------|
| Compound of formula I         | 3.0 mg    |
| Gelatine                      | 150.0 mg  |
| Phenol                        | 4.7 mg    |
| Water for injection solutions | ad 1.0 ml |

Claims

## 1. Compounds of formula (I)



wherein

- 5 U is O or a lone pair,
- V is a) O, S,  $\text{NR}^1$ , or  $\text{CH}_2$ , and L is lower-alkylene or lower-alkenylene,  
b)  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ , and L is lower-alkylene or a single bond,
- W is CO, COO,  $\text{CONR}^2$ , CSO,  $\text{CSNR}^2$ ,  $\text{SO}_2$ , or  $\text{SO}_2\text{NR}^2$ ,
- X is hydrogen or one or more optional halogen and/or lower-alkyl substituents,
- 10 m is 1 or 2,
- n is 0 to 7,
- $\text{A}^1$  is hydrogen, lower-alkenyl, or lower-alkyl optionally substituted by hydroxy, lower-alkoxy, or thio-lower-alkoxy,
- $\text{A}^2$  is cycloalkyl, cycloalkyl-lower-alkyl, lower-alkenyl, lower-alkinyl, or lower-alkyl optionally substituted by hydroxy, lower-alkoxy or thio-lower-alkoxy,
- 15  $\text{A}^3$  and  $\text{A}^4$  independently from each other are hydrogen or lower-alkyl, or  $\text{A}^1$  and  $\text{A}^2$  or  $\text{A}^1$  and  $\text{A}^3$  are bonded to each other to form a ring and  $-\text{A}^1-\text{A}^2-$  or  $-\text{A}^1-\text{A}^3-$  are lower-alkylene or lower-alkenylene, optionally substituted by  $\text{R}^3$ , in which one  $-\text{CH}_2-$  group of  $-\text{A}^1-\text{A}^2-$  or  $-\text{A}^1-\text{A}^3-$  can optionally be replaced by
- 20  $\text{NR}^4$ , S, or O,
- $\text{A}^5$  is cycloalkyl, cycloalkyl-lower-alkyl, heterocycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, lower-alkyl optionally substituted with hydroxy or lower-alkoxy, alkenyl optionally substituted with hydroxy, or alkadienyl optionally substituted with hydroxy,
- 25  $\text{R}^3$  is hydroxy, lower-alkoxy, thio-lower-alkoxy,  $\text{N}(\text{R}^5, \text{R}^6)$ , or lower-alkyl optionally substituted by hydroxy,

$\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^4$ ,  $\text{R}^5$ , and  $\text{R}^6$  independently from each other are hydrogen or lower-alkyl, and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

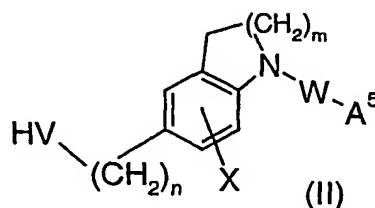
2. Compounds according to claim 1, wherein U is a lone pair.
3. Compounds according to any of claims 1 to 2, wherein V is O or CH<sub>2</sub> and L is lower-alkylene or lower-alkenylene.
4. Compounds according to any of claims 1 to 2, wherein V is -C≡C- and L is  
5 lower-alkylene or a single bond.
5. Compounds according to any of claims 1 to 4, wherein n is 0.
6. Compounds according to any of claims 1 to 5, wherein A<sup>1</sup> is lower-alkyl.
7. Compounds according to any of claims 1 to 6, wherein A<sup>1</sup> is methyl or ethyl.
8. Compounds according to any of claims 1 to 7, wherein A<sup>2</sup> is lower-alkenyl, or  
10 lower-alkyl optionally substituted by hydroxy or lower-alkoxy.
9. Compounds according to any of claims 1 to 8, wherein A<sup>2</sup> is 2-propenyl or 2-hydroxy-ethyl.
10. Compounds according to any of claims 1 to 5, wherein A<sup>1</sup> and A<sup>2</sup> are bonded to each other to form a ring and -A<sup>1</sup>-A<sup>2</sup>- is lower-alkylene or lower-alkenylene, optionally  
15 substituted by R<sup>3</sup>, in which one -CH<sub>2</sub>- group of -A<sup>1</sup>-A<sup>2</sup>- can optionally be replaced by NR<sup>4</sup>, S, or O, wherein R<sup>3</sup> and R<sup>4</sup> are as defined in claim 1.
11. Compounds according to any of claims 1 to 10, wherein A<sup>3</sup> is hydrogen.
12. Compounds according to any of claims 1 to 11, wherein A<sup>4</sup> is hydrogen.
13. Compounds according to any of claims 1 to 12, wherein A<sup>5</sup> is cycloalkyl,  
20 cycloalkyl-lower-alkyl, heterocycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, or lower-alkyl optionally substituted with hydroxy or lower-alkoxy.
14. Compounds according to any of claims 1 to 13, wherein A<sup>5</sup> is phenyl or benzyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluorine and chlorine, or wherein A<sup>5</sup> is lower-alkyl.
- 25 15. Compounds according to any of claims 1 to 14, wherein A<sup>5</sup> is phenyl, 4-fluorophenyl, 4-chloro-phenyl, butyl, or pentyl.
16. Compounds according to any of claims 1 to 15, wherein W is COO, CONR<sup>2</sup>, CSO, or CSNR<sup>2</sup>, and R<sup>2</sup> is hydrogen.



17. Compounds according to any of claims 1 to 16, wherein X is hydrogen.
18. Compounds according to any of claims 1 to 16, wherein X is fluorine.
19. A compound according to any of claims 1 to 18, selected from the group consisting of
- 5 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid O-(4-chloro-phenyl) ester,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl  
10 ester,  
6-[4-(Allyl-methyl-amino)-but-2-enyloxy]-3,4-dihydro-2H-quinoline-1-carboxylic acid (4-fluoro-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid 4-fluoro-benzylamide,  
15 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid 4-chloro-benzylamide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid (4-fluoro-phenyl)-amide,  
5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid O-(4-fluoro-phenyl) ester,  
20 5-[5-(Allyl-methyl-amino)-pentyl]-2,3-dihydro-indole-1-carbothioic acid (4-chloro-phenyl)-amide,  
5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid (2-methyl-butyl)-amide, and  
25 5-[4-(Allyl-methyl-amino)-butoxy]-2,3-dihydro-indole-1-carbothioic acid butylamide,  
and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.
20. A compound according to any of claims 1 to 18, selected from the group consisting of
- 5-[5-(Allyl-methyl-amino)-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-  
30 chloro-phenyl ester,  
5-[5-[Ethyl-(2-hydroxy-ethyl)-amino]-pent-1-ynyl]-6-fluoro-2,3-dihydro-indole-1-carboxylic acid 4-chloro-phenyl ester,  
6-Fluoro-5-[5-(methyl-propyl-amino)-pentyl]-2,3-dihydro-indole-1-carboxylic acid phenyl ester,  
35 and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

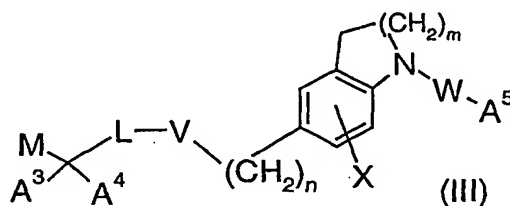
21. A process for the manufacture of compounds according to any of claims 1 to 20, which process comprises

a) reacting a compound of formula (II)



- 5 with a compound  $(A^1, A^2, U)N-C(A^3, A^4)-L-M$ , wherein V is O, S or  $NR^1$ , M is mesylate, tosylate, triflate, Cl, Br or I, and U,  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , L, W, X, m, n and  $R^1$  are as defined in claim 1, or wherein HV is mesylate, tosylate, triflate, Cl, Br or I, and M is OH, SH or  $NHR^1$ , and  $R^1$  is as defined in claim 1,

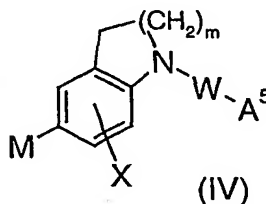
or b) reacting a compound of formula (III)



10

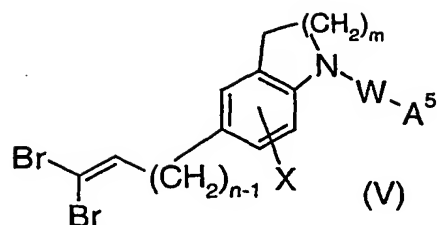
with a compound  $NHA^1, A^2$ , wherein M is mesylate, tosylate, triflate, Cl, Br or I, and  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , L, V, W, X, m and n are as defined in claim 1,

or c) reacting a compound of formula (IV)



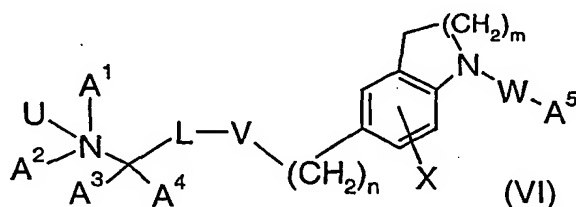
- 15 with a compound  $(A^1, A^2, U)N-C(A^3, A^4)-L-C\equiv CH$ , wherein M is Br or  $F_3CO_2SO$ , and U,  $A^1$ ,  $A^2$ ,  $A^3$ ,  $A^4$ ,  $A^5$ , L, W, X and m are as defined in claim 1,

or d) reacting a compound of formula (V)



with a compound  $(A^1, A^2, U)N-C(A^3, A^4)-L-M$ , wherein M is mesylate, tosylate, triflate, Cl, Br or I, and  $A^1, A^2, A^3, A^4, A^5, W, U, L, X, m$  and  $n$  are as defined in claim 1,

or e) hydrogenating a compound of formula (VI)



5

wherein V is  $-C\equiv C-$ , and  $A^1, A^2, A^3, A^4, A^5, U, W, L, X, m$  and  $n$  are as defined in claim 1,

and optionally converting a compound according to any of claims 1 to 20 to a pharmaceutically acceptable salt,

and optionally converting a compound according to any of claims 1 to 20, wherein U is a lone pair, to a corresponding compound wherein U is O.

10

22. Compounds according to any of claims 1 to 20 when manufactured by a process according to claim 21.

23. Pharmaceutical compositions comprising a compound according to any of claims 1 to 20 and a pharmaceutically acceptable carrier and/or adjuvant.

24. Compounds according to any of claims 1 to 20 for use as therapeutic active substances.

15

25. Compounds according to any of claims 1 to 20 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with OSC.

20

26. A method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative

disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method comprises administering a compound according to any of claims 1 to 20 to a human being or animal.

27. The use of compounds according to any of claims 1 to 20 for the treatment  
5 and/or prophylaxis of diseases which are associated with OSC.

28. The use of compounds according to any of claims 1 to 20 for the treatment  
and/or prophylaxis of hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular  
diseases, mycoses, parasite infections, gallstones, tumors and/or hyperproliferative  
disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance, and  
10 diabetes.

29. The use of compounds according to any of claims 1 to 20 for the preparation  
of medicaments for the treatment and/or prophylaxis of diseases which are associated with  
OSC.

30. The use of compounds according to any of claims 1 to 20 for the preparation  
15 of medicaments for the treatment and/or prophylaxis of hypercholesterolemia,  
hyperlipemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones,  
tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of  
impaired glucose tolerance and diabetes.

31. The novel compounds, processes and methods as well as the use of such  
20 compounds substantially as described hereinbefore.

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## INTERNATIONAL SEARCH REPORT

Inte: d Application No

PC1/CT 01/14620

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/58 C07D215/20 C07D209/08 A61K31/47 A61K31/404

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.          |
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| A          | WO 93 12754 A (ABBOTT LAB)<br>8 July 1993 (1993-07-08)<br>see whole document, specially examples<br>36,96 and general formula<br>-----<br>-/--                                       | 1-31                           |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

4 March 2002

Date of mailing of the international search report

11/03/2002

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## INTERNATIONAL SEARCH REPORT

Inte

Application No

PC

01/14620

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
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| A          | EP 0 318 860 A (BANYU PHARMA CO LTD)<br>7 June 1989 (1989-06-07)<br>the whole document<br>---   | 1-31                  |
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| A          | EP 0 636 367 A (HOFFMANN LA ROCHE)<br>1 February 1995 (1995-02-01)<br>cited in the application<br>the whole document<br>-----                     | 1-31                  |

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-18,21-31 (partly)

Present claims 1-18,21-31 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 1 wherein A1 and A2 are alkyl or alkenyl or alkynyl, possible substituted, the cyclisation of A1 and A3 or A1 and A2 is not allowed and the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 01/14620

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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